

TITLE:-

The Nature of Bell's palsy: its aetiology, and the role of
Herpes Simplex Virus

By:-

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Mocha Pot Showing a Right
Sided Facial Weakness



Although the cause is "unknown" this should not be confused with the term "idiopathic" facial paralysis (which when acute constitutes a Bell's palsy). Such a term may only be used after a careful clinical and scientific enquiry has failed to reveal a primary cause.

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Dedication:-

to Margaret and Alice

Acknowledgements

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STATEMENT OF ORIGINALITY

I hereby declare that (a) this thesis was my own composition; and (b) that the thesis contains an account of studies designed, executed and analysed by myself with partial resource to assistance of a specialised nature with processing the specimens in the DNA/DNA hybridization study; statistical advice and secretarial and computing assistance.

Ian Williamson

GLOSSARY OF TERMS

ACTH	Adrenocorticotrophic hormone
AGVS	Acute gingivo stomatitis
A.I.	Amersham International
AICA	Anterior inferior cerebellar artery
BAM H ₁	Bacterial Ampicillin (Resistance marker) H ₁ plasmid
B.P.	Bell's palsy
bp	Base pair
B.S.S.	Balanced salt solution
C.F.	Complement fixing
C.I.	Confidence interval
CMV	Cytomegalovirus
CNS	Central nervous system
CPAF	Chlorpropamide-alcohol flushing
CPE	Cytopathic effect
CSF	Cerebrospinal fluid
CSM	Committee on Safety of Medicines
d.f.	Degrees of freedom
DHA	District Health Authority
DNA	Deoxyribonucleic acid
ECo R ₁	Escherichia Coli R ₁ plasmid
FPC	Family Practitioner Committee
G.H.	Growth hormone
GTT	Glucose Tolerance Test
HLA	Histocompatibility locus antigen (human leukocyte antigen)
HSV	Herpes simplex virus
HSV ₂	Herpes simplex virus (type II)
HSV ₁	Herpes simplex virus (type I)
IBM	International Business Machines
IFN	Interferon
I.R.	Immuno-reactive
JANET	Joint Academic Network
L ₁₅	Leibowitz ₁₅ medium
L.H.	Luteinizing hormone
LMN	Lower motor neurone
M.C.	Medium change
mm	Millimetre
M.R.I.	Manchester Royal Infirmary

N.B.L.	Northumbria Biological Laboratories
NIDD	Non-insulin dependent diabetes
OPCS	Office of Population and Census Surveys
p	rho, (significance)
P ₃₂	Phosphorus (atomic wt 32)
Pen V.	Phenoxymethyl Penicillin (V)
POMC	Pro opiomelanocortin (Big ACTH)
RNA	Ribonucleic acid
SDS	Sodium dodecyl sulphate
SPSSX	Statistical Package for Social Scientists, X ₁
SRE	Schedule of Recent Events
SSC	Sodium chloride/sodium citrate
T _K	Thymidine kinase
URTI	Upper respiratory tract infection
U.v.	Ultraviolet
V	vero
VZV	Herpes zoster/Varicella zoster virus

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ABSTRACT

This thesis aims to investigate the nature and aetiology of Bell's palsy by studying its natural history and epidemiology in general practice, and by means of virological studies.

A new hypothesis is outlined of the aetiology of Bell's palsy which provides a framework for the investigations:-

"Bell's palsy is due to a reactivation of HSV in the geniculate ganglion. During this process, neurotransmitters (opioid peptides) and interferon are produced. These cause local vaso-dilation and damage, particularly to the suprageniculate part of the facial nerve."

This thesis is concerned principally with testing the first part (sentence) of this hypothesis.

The virological studies set out to examine a possible role for HSV in Bell's palsy, which is contingent on the belief that HSV is normally resident or resident to some degree in the geniculate ganglia of the general population. The evidence of the DNA/DNA hybridization study suggests that HSV may be ubiquitously present in human cadaveric geniculate ganglia. From these a substantial proportion might be expected to reactivate. In contrast the observed incidence of Bell's palsy in the descriptive study of 16.4 per 100,000 per year suggests that if HSV is a cause the mere occurrence of reactivation is an inadequate explanation of the disease mechanism.

The epidemiological studies describe Bell's palsy in British general practice where cases are less strongly selected than in hospital studies. By means of a case-control study and match-pair analysis further investigations are made as to the effect of different factors including various types of stress in the aetiology of Bell's palsy. The results of these studies suggest numerous aetiological agents, of particular relevance to the hypothesis are genetic factors, states of increased "stress" and opioid "sensitivity", which are discussed.

In conclusion the balance of evidence is compatible with the proposed hypothesis, which in the author's opinion justifies further research, especially since it carries treatment implications.

CHAPTER 1

Introduction

1.1 Introduction and Definition

To explore the aetiology of Bell's palsy is to explore a fascinating labyrinth for Nature's clues.

Bell's palsy is named after Sir Charles Bell who first drew attention to the distribution and function of the facial nerve in 1821. Clinically it is an acute lower motor neurone lesion. The lesion may be sited anywhere peripheral to and including the facial nerve motor nucleus, or by contiguity affect the nerve along this route. Bell's palsy is an 'exclusion diagnosis' and represents between 28-80% of all causes of facial paralysis (Alberti 1972, Zulch 1970).

It is widely accepted that the cause or causes of Bell's palsy, also known as acute idiopathic facial paralysis are unknown. This remains so despite considerable research, effort, debate and ingenious speculation into its cause or causes. One hesitates before adding to such a weight of literature.

'Nature is conservative', it adheres to its own consistent mechanisms or active processes. Could Bell's palsy have but one mechanism though its causes may be diverse? The search for uniformity characterizes the empirical scientific approach. It is worth pursuing in the aetiological debate surrounding Bell's palsy; though many probably rightly claim its causes are 'legion', it does not follow that its mechanism is.

Zulch states, "an unambiguous explanation may never be forthcoming: different factors may be capable of triggering the same mechanism". His comments reflect contemporary understanding. The fact that there is extensive speculation as to the aetiology of Bell's palsy is indicative that no theory is sufficiently convincing, or is able to resolve conflicting interpretations of clinical and experimental work. The aetiology must be one which can produce a sudden facial paralysis with a high probability of a full spontaneous recovery. It should also explain why the incidence of recurrent disease is low - less than 10% (Park 1949, Peiterson 1982, Yanagihara 1984, Pitts 1988).

Bell's palsy also attracts wider controversy. Ambiguities of definition remain. Should Bell's palsy be considered a mono- or poly-neuropathy? Is the lesion sited in the intratemporal portion of the facial nerve, in the brain-stem or both? Should the presence of diabetes result in its exclusion from this diagnostic group, or is Bell's palsy sometimes a diabetic mono-neuropathy?

In 1916 Patrick observed facial diplegia with polyneuritis and questioned the clinical dividing line with Bell's palsy diplegia (paralysis ex-frigore). In 1919 Antoni suggested Bell's palsy was a sub-category of acute infectious polyneuritis and described 5 patients with Zoster vesicles who had facial paralysis and polyneuritis. This idea is further supported by Friedman 1970 and McCormick in 1972. Adour in 1978 in a study of 150 patients with Bell's palsy noted a high incidence of other cranial nerve involvement. Of 48 consecutive patients in this series, 19% had a trigeminal involvement, 19% had glossopharyngeal involvement and a further 29% had both nerves involved. The author states that, "the basic problem is a lack of understanding that acute facial paralysis is not a localised disease of the 7th cranial nerve but a variant of acute benign cranial polyneuritis". In this context it would have been more correct to state, "not confined to the 7th cranial nerve", rather than 'localised', as evidence exists for an anatomically discrete lesion of the 7th nerve in Bell's palsy patients. Fisch's findings of damming of axoplasm with an electroneurographic block (obtained at operation) at the narrow entrance to the Fallopian canal incriminates the suprageniculate part of the Facial Nerve in patients with acute Bell's palsies (Fisch 1982). This has proved a fascinating but contested observation. However further support has come from O'Donoghue at Oxford who also noted damming of axoplasm at the entrance to the Fallopian canal (O'Donoghue 1985). Esslen (1977) postulates that local anatomical factors provide congruence for palsies of different aetiologies, and suggests the term acute facial palsies of meato-labyrinthine localization, as a substitute for the term Bell's palsy.

In an Israeli study Korczyn 1971 found abnormal glucose tolerance tests or overt diabetes in 66% of 130 Bell's palsy patients. Pecket in 1982 postulated that Bell's palsy should be considered as a diabetic mononeuropathy. It could be argued that a facial paralysis associated with diabetes cannot be idiopathic as it is secondary to diabetes.

Conversely to exclude the diabetic group is to presume Bell's palsy cannot occur in diabetics. It is against such a background and uncertainties that any aetiological theory has to be measured.

1.2 Historical Review of Aetiological Theories

Sir Charles Bell, surgeon to the Middlesex Hospital and principal of the Great Windmill Street School of Anatomy first drew attention to the anatomical features and function of the 7th cranial nerve. He described it as the respiratory nerve in order to emphasize what he thought was its main function. In a book on the nervous system Bell (1830, revised 1883), later outlined his collected works on the facial and other nerves (principally the 5th). With time Bell's name became attached to facial paralysis, and initially described all cases of facial paralysis no matter what the cause.

In 1836 Berard postulated that a "rheumatic neuritis" in which the swollen nerve pressed against the walls of the Fallopiian canal, was the cause of Bell's palsy.

In 1909 Ramsay-Hunt described hypoaesthesia of the face in association with 'refractory facial paralysis'. Interestingly the trigeminal (5th cranial) nerve was not implicated at the time, even though Sir Charles Bell had by then defined the sensory function of the 5th nerve. It was believed that denervation of stretch-receptors in facial muscles must account for this symptom. However since they have only been found in the extrinsic ocular muscles such a statement would appear to be stretching credulity! Numbness of the face is however an ambiguous term for patients and needs careful interpretation.

Some of the earliest aetiological concepts of Bell's palsy centred around the idea that it was secondary to a sub-clinical infection of the middle-ear space. This was proposed by Reik in 1904. He recommended that all patients with the disease be seen by an 'aurist'. These studies demonstrate the importance of excluding middle ear pathology, and indeed other pathology along the course of the nerve in Bell's palsy. Bell's palsy has become redefined with advances in understanding; the diseases to which facial paralysis is secondary have grown leaving the idiopathic* group to become smaller.

* Gr. ἰδιοπαθεια, Galen 1640 - a disease not preceded or occasioned by any other, a primary disease.

1.2.1 The cold hypothesis - a or ex-frigore

This is one of the hypotheses accepted by Sir Charles Bell, namely that exposure to draught or chill results in a paralysis. This is still supported by Zulch (1970) who believes rapid cooling or chilling may produce Bell's palsy. Other writers refute these findings. In a review of this theory by Diamond and Frew (1979) the authors state "The enclosure of the nerve in the Fallopian canal should be a protective advantage as far as cold injury is concerned, and the adjacent cranial and cervical nerves would appear to be immune from this proposed lesion". This line of thinking presumes that cold injury may only be direct, and ignores the possible effect of the body's physiological response to cold-stress. Although it may be argued that few physicians today take this theory seriously, some respect should be afforded to a traditional explanation in the author's view.

1.2.2 Genetic factors

Although it has long been known that Bell's palsy tends to run in families (see p.142) very few control studies have been done. Recent interest has centred on a possible association of certain HLA types, particularly BW67 and Bell's palsy (Shibahara 1988).

1.2.3 Vascular theories

In 1936 Audibert proposed that vascular factors e.g. thrombosis or vasospasm, could be aetiologically linked with Bell's palsy. He was further supported by Kettel in 1947. Later Hilger in 1949, Sullivan and Smith in 1950 and also Blunt 1956, concurred with the belief that an initial local vasospasm occurred in the region of the external carotid and its branches to the mastoid segment of the nerve. The result was primary ischaemia which produced transudation and a rise in intraneural pressure. This caused a block, or impedance of the arterial blood supply to a larger segment of the facial nerve, and secondary ischaemia sufficient to produce the symptom of paralysis.

Motivated by the belief in a primary vascular cause, Cawthorne and Haynes (1956) advocated surgical decompression of the nerve (mastoid segment), as treatment in selected cases. Whatever the merits of this technique there is no doubt that surgical exposure of the nerve throughout its intratemporal course has yielded much useful, though often conflicting, information.

Early attention centred on decompressing the mastoid segment, and later the vertical and suprageniculate parts of the facial nerve. The modern view is that the disease process occurs most often at the entrance to the Fallopian canal (Fisch 1982), with the labyrinthine portion of the facial nerve being supplied by branches from the anterior inferior cerebellar artery (A.I.C.A.); and branches from the petrosal and geniculate ganglion arteries.

Cervical sympathectomy enjoyed a short vogue as a surgical treatment for Bell's palsy. It was introduced by Korkis in 1959. Fearnley in 1964 demonstrated that cervical sympathetic block was of no value - a disappointing finding in terms of treatment, and a difficult one to explain if vasospasm were involved (with the lesion lying in the territory of the external carotid).

Janetta in 1978 postulated that Bell's palsy is due to the facial nerve being compressed by a loop of A.I.C.A., suddenly shifting in the cerebello-pontine angle and stretching the nerve. Such may be the case in a small percentage of Bell's palsies: but it is surely limited as an explanation in being perhaps too "accidental", and in the detail which it fails to embrace.

A vascular aetiology is also supported by such independent authorities as Bosatra 1956, Fowler 1958, Williams 1959, Kettel 1959, Jongkees 1972, Miehlike 1973 and Calcaterra 1976.

In support of a vascular aetiology are the sudden onset of the paralysis, usually in several hours, although acute demyelination of viral onset may also be rapid; and lack of a marked cellular infiltration in most pathological studies. The suprageniculate localization of the lesion, as estimated by nerve conduction studies, cannot be explained so easily by a demyelination model. The central/peripheral myelin junction is near the brain-stem in motor nerves and does not coincide with the proximal level of nerve block observed by Fisch.

Although animal experiments and clinical studies exist (Calcaterra 1976), which show that ligation or embolization of the arterial supply to the facial nerve produces a paralysis, to say this is the cause of Bell's palsy is to confuse what is possible with what is probable.

Bell's palsy patients do not appear to be suffering from thromboembolic disease nor if vasospasm is the cause is the frequency of recurrent attacks as high as would be predicted for such a mechanism (cf. migraine and Raynaud's disease).

In conclusion and despite the appeal of some aspects of vascular theories, it must be stated that firm evidence for a primary vascular cause of Bell's palsy is lacking.

1.2.4 Immunological theories

Immunological theories concentrate on the mechanism of nerve injury and not the causes. Some authors believe Bell's palsy to be a forme fruste of Guillain-Barré syndrome - although CSF protein levels are normal in Bell's palsy patients. Charous and Saxe noted in 1962 that oedema of the 7th nerve and degeneration was present in both conditions. They further remarked that both have a spontaneous onset and rapid recovery, often with preceding symptoms of a viral illness. The observation of multiple cranial nerve involvement in Bell's palsy lends further weight.

The main proponent of the auto-immune theory is McGovern who in 1966 published results of animal experiments. The facial nerves of dogs sensitized to horse serum showed a more severe facial paralysis with histological evidence of more severe nerve damage after injection of saline, horse serum, and epinephrine into the Fallopian canal than in non-sensitized dog controls. The intensity of oedematous response appeared to be related to the loss of perivascular mast-cells (McGovern 1977).

In 1975 Abramskey noted the lymphocyte response to neural antigen PIL was positive in in-vitro studies in Bell's palsy patients and Guillain-Barré patients only. 26 control patients with 7th nerve palsies of different aetiologies were all negative.

In 1982 McGovern put forward the idea that Bell's palsy should be considered an "immunopathophysiological" reaction. The reaction is one of immediate-type hypersensitivity in which "the role of the mast cell and the release of vasoactive amines induced by antigen-IgE interaction, and other immune-complexes are well understood". He further cites experimental evidence of the control of neural oedema

by the use of cromolyn sodium.

1.2.5 Viral theories

The viral hypotheses gain most weight from the fact that some facial palsies are undoubtedly produced by viruses. Some authors believe Bell's palsy is a Herpes Zoster (VZV) infection without an auricular rash, a more cryptic variant of Ramsay-Hunt syndrome (Herpes Zoster oticus). Aitken and Brain in 1933 demonstrated complement fixing antibodies to VZV in 4 of 22 cases of Bell's palsy without a rash. Mair in 1976 found 9 of 133 patients with peripheral facial palsy to have elevated VZV antibody levels. 7 of these patients were Ramsay-Hunt syndromes but 2 had neither a rash or auditory symptoms. Djupesland (1977) found evidence of elevated VZV antibody levels in 9 of 51 patients and Tomita in 1972 found evidence of rising titres in 18% of 247 patients. However Berg in 1976 in 44 patients found VZV antigen only in those patients with Ramsay-Hunt syndrome.

Other viruses incriminated by antibody studies include Influenza A (Brodie 1979), Influenza B (Djupesland 1977), Mumps (Saunders 1959), Rubella (Fowler 1963), Adenovirus (Brodie 1979), RSV (Brodie 1979), Mycoplasma P1 (Brodie 1979), Polio (Menkes 1974), HTLV (Wiselka 1987). Herpetoviridae include CMV (Mair 1983), E.B.V. (Grose 1973, Mendonca 1973, Weintraub 1976) and HSV which will be discussed later. One patient in this study developed a Bell's palsy after taking the polio-Sabin vaccine (see case report p.124).

Viral theories have found further support from Djupesland (1977), who performed C.S.F. studies and found a mild lymphocytic pleocytosis with moderately elevated proteins.

Some antibody studies have shown negative results and these include Dodge and Pokanzer 1962, McCormick 1972 and Korczyn 1973, Mees 1981, Traavik 1983. Viral culture and electron microscopy studies of geniculate ganglion cells in one Bell's palsy patient showed no evidence of growth or nuclear structures compatible with HSV or CMV viruses (Palva 1978). Even when results are taken from those studies showing most positive results, still approximately 1/3rds of cases show no evidence of a recent viral infection.

Aviel in 1983 studied 32 patients with Bell's palsy by measuring serum alpha interferon levels in patients who showed no evidence of acute intercurrent viral infection. 66% had higher than normal IFN levels (normal < 16 u/ml) at the first examination. During the first three days IFN levels were highest (mean 95 u/ml) with a sharp decline on the 4-6th days, and a return to normal values from the 7th day onwards. Antibody levels to HSV and VZV did not show any changes at repeated examinations. Aviel concludes that an unusual virus may be the cause, or a latent reactivation of HSV should be considered. Jonsson (1989) found that the content of IFN in the serum of patients with Bell's palsy was increased in both acute ($n = 46$ $p < 0.5$) and convalescent ($n = 46$ $p < 0.05$) stages as compared with 17 control subjects. He concludes that this may indicate a low-grade antiviral response that may reflect the reactivation of a viral infection.

With respect to a route of entry into the C.N.S., Blatt (1966) proposed that an ascending viral agent entered through taste receptors to produce inflammation of the chorda tympani nerve. May (1978) suggested that a viral agent could lead to the observed retrograde pathology producing strangulation of the facial nerve in the Fallopian canal. This route may be particularly important when considering HSV as a cause.

It is worth remembering that other infectious agents than viruses may produce apparently idiopathic facial paralysis e.g. Lyme disease - *Borrelia burgdorferi*, which is one of the commoner causes in the New Forest area.

1.3 Origins of Present Studies

1.3.1 HSV as a cause of Bell's palsy?

Herpes Simplex Virus (type I) was first postulated as a cause of Bell's palsy by McCormick in 1972. He based his theory largely on the evidence of experimental animal work which described the behaviour of HSV in the nervous system. However he believed HSV to "reside" in the axon of the peripheral nerve where it was unaffected by neutralizing antibody, and from which it subsequently 'ruptured'. It is the modern view however to implicate the ganglia rather than the axon as the favoured site of residency by HSV. Adour in 1975 and 1978, using evidence from antibody and epidemiological studies further developed the idea of herpes simplex

reactivation as a cause of Bell's palsy. Adour states "we looked by computer-assisted statistical methods for a factor that could cause polyneuritis, and that could be found in all of our patients with Bell's palsy. The only factor common to all patients tested for its presence were antibodies to herpes simplex virus". He further notes that a high but stationary titer to herpes virus is seen in recurrent or reactivated herpes virus infection. Adour interprets his work as being commensurate with HSV reactivation occurring in patients with Bell's palsy, and points to a lack of evidence to support the notion of a primary infection, although sporadic reports do occur in the literature (Smith 1987, Ghonim 1988). Vahlne in 1981 using C.F., envelope-antigen radioimmunoassay and capsid-antigen radioimmunoassay in 142 cases and 53 controls came to similar conclusions as Adour. IgM levels showed no statistical difference between the groups.

Adour noted from his epidemiological studies that Bell's palsy like cold sores (a recrudescence of HSV infection), was associated with menstruation, pregnancy, stress and preceding respiratory infection. Adour (1978) quoting his own work (1975, 1976) states "these studies indicate rather conclusively that herpes simplex virus is causative in idiopathic facial paralysis". His findings are of considerable interest but his assertions lack validity. Firstly he presents no evidence that the association is a causative one. Secondly on probability grounds the high prevalence of HSV in the indigenous population, > 90% by the 4th decade of life (Nahamias 1973), mitigates against a straightforward argument. Thirdly the epidemiological study was based on a pre-selected group (insurance based) operating within the terms of an American open-access type referral system. Fourthly a point of confusion in Adour's work appears to be that he does not emphasize herpes labialis as a recrudescence of HSV, a process which must include reactivation of HSV and other active processes (asymptomatic viral shedding has a point prevalence of 5% in the general population - reactivations are relatively common without demonstrable e.g. cold sore lesions). Adour's analogy between neural reactivation of HSV in Bell's palsy and cold sore lesions, thus remains arguably inspired guesswork. Nonetheless despite these objections the findings are of sufficient importance to warrant further investigation.

Table 1: Review of Serological Tests for HSV in Bell's Palsy

Principal Author	Year	Number of Subjects	Method of Examination	% of Patients with Significant Results
Tomita	1972	44 Bell's palsy	CF	6.8%
Korczyn	1973	150 Bell's palsy	CF	0.0%
Juji	1974	143 Bell's palsy	CF	0.0%
Adour	1975	41 Bell's palsy	CF	0.0%
	1978	41 Bell's palsy	CF	0.0%
Djupestrand	1975	33 Bell's palsy	CF	3.0%
	1976	51 Bell's palsy	CF	2.0%
Berg	1976	33 Bell's palsy	CF	0.0%
Mori	1977	129 Bell's palsy	CF	8.5%
	1979	129 Bell's palsy	CF	8.5%
Saito	1977	257 Bell's palsy	CF	8.6%
Gotlieb-Stematsky	1978	4 Bell's palsy	CF	25.0%
Brodie	1979	74	CF	17.7%
Muto	1980	67 Bell's palsy	CF	4.5%
Tovi	1980	70 APFP	ELISA	1.4%
Mees	1981	14 Bell's palsy	ELISA	0.0%
Vahlne	1981	81 Bell's palsy	CF	6.2%
Mertens	1982	32 APFP	CF	6.3%
Hadar	1983	153 Bell's palsy	IPAMA	0.0%
Jamal & Al-Husini	1983	28 Bell's palsy	HI	0.0%
Mair & Traavik	1983	88 APFP	CF	0.0%
Traavik	1983	65 APFP	CF	0.0%
Honda	1985	80 Bell's palsy	CF	1.3%
Nakamura	1988	45 Bell's palsy	CF	2.2%
			NT	15.6%

Key:- CF - complement fixation test
 ELISA - enzyme linked immunosorbent assay
 APFP - acute peripheral facial palsy (includes Bell's palsy and Ramsay Hunt)
 IPAMA - immunoperoxidase antibody - membrane antigen technique
 HI - haemagglutination inhibition test
 NT - neutralizing antibody test

The hypothesis of HSV reactivation is very difficult to either prove or disprove. Biopsy of the facial nerve in patients suffering from facial paralysis is not an ethical approach, although the geniculate ganglion and chorda tympani nerve have been biopsied. Thus far the Koch-Henlé postulates for an infective cause of Bell's palsy remain unfulfilled. No infective agent has been constantly associated with the pathological condition or found "mostly but not inevitably in the lesions". In Bell's palsy such verification may be limited by having a number of aetiological agents rather than being a single disease entity.

Antibody studies often the mainstay in confirming a specific viral aetiology are problematical when studying a reactivation rather than primary infection of herpes simplex. This is because:-

- a) Most of the population under study are over 30 yrs old with high C.F. antibody levels to HSV in this group approaching 100%. (Nahamias 1973).
- b) A rise in level may indicate infection elsewhere e.g. cold sores, genital herpes, keratitis etc.
- c) It is well established that reactivations of the virus (neural) may occur without a demonstrable rise in antibody levels which are often already high (Ross 1975, Corey 1986).

Nonetheless many workers have examined for HSV using serological tests in Bell's palsy patients. See table (1) opposite.

General support for the HSV reactivation hypothesis is gained from HSV induced demyelination in animal models; the rabbit-eye 5th nerve model (Kristensson 1979) ; and the mouse-ear model (Hill 1983). The lesions produced show broad similarities with those observed in Bell's palsy. Neither animal is a natural host of herpes simplex, and such artificiality should be considered in extrapolating to the situation in human HSV infection. Vahlne in 1985 further discusses HSV induced demyelination in animals as a model for Bell's palsy and also other diseases such as multiple sclerosis.

Most recently in 1988 Thomander using a mouse-tongue model successfully isolated HSV from the geniculate ganglion. He writes that 3 days

after inoculation "50% of the facial nerves, 30% of the trigeminal ganglia and all brain stems were infected. Because of difficulty with the dissection of the temporal bones, it is most probable that the geniculate ganglion was not obtained from all animals".

A possible method to test the hypothesis of HSV reactivation arises from observations in human post-mortem sensory ganglia. Baringer first isolated HSV from human trigeminal ganglia by co-cultivation in 1972. Since then a number of workers have isolated herpes simplex from other primary afferent sensory ganglia including the vagus, cervical sympathetic, thoracic, coeliac and sacral ganglia by a variety of techniques.

To date there has been no successful isolation or detection of HSV from the geniculate ganglion (obtained from temporal bones), or from the facial nerve in humans. The finding of the virus in the geniculate ganglion indicating persistence (latency) in the normal population would in the author's view allow the advancement of HSV reactivation, as a cause of Bell's palsy as a more substantial hypothesis, since the virus must be latent in a proportion of the normal population if it is subsequently to reactivate. If however the virus could not be identified at such a site using a reliable control method, this would be against such a hypothesis, to quote Popper's dictum the "hypothesis would be falsified". (This argument is expanded under aims and objectives, p. 40).

A criticism of the above method might be that although Adour explicitly states HSV reactivation is the mechanism in Bell's palsy, this notionally might occur in other afferent sensory ganglia or at other sites in the C.N.S. Immunological damage at a distance from the culpable ganglion whilst leaving its immediate environment relatively intact would appear to be an unnecessary embellishment of such a theory. Especially since aetiologically Bell's palsy must by definition affect the facial nerve at least more often than any other cranial nerve. Thus in the author's opinion possible residency of HSV in the C.N.S. with respect to Adour's hypothesis and his own, is respectively best, and must be tested at this site (geniculate ganglia). Since Adour's supporting observations stem primarily from observations about recrudescence of HSV (cold sores), then he is in fact using a model of local destruction by HSV virus. Surely for his analogy to be valid some predominantly local mechanism of tissue destruction is still required in the C.N.S. This seems to

the author an inconsistency in Adour's apparent distaste for the evidence which implicates the facial nerve in the proximity of the geniculate ganglion in most instances.

The technique to be employed by the author, co-cultivation and DNA probing are however less sensitive methods than serological tests.

1.3.2 The need for further epidemiological studies

There is a need for Adour's work to be repeated by an epidemiological study from this country. What information is available about the natural history of Bell's palsy has come primarily from hospital studies such as Brodie's (1979), with only sporadic reports coming from general practice (Grout 1977, Presley 1978). Seymour (quoted by Fish 1977) states:- "Because of the lack of adequate record keeping for this type of disease in Australia, I attempted to obtain information regarding treatment and incidence by sending a questionnaire to 3,000 of our general practitioners. This has been done because the practitioner treats primarily Bell's palsy".

As yet no study from this country has looked at the natural history of Bell's palsy by using a case-finding method involving large numbers of general practitioners. Combined with a case-control study and match-pair analysis Adour's findings can be further tested. Such a study would also have the advantage of describing the natural history in a different type of population than is usually examined in hospital studies.

1.3.3 The value of a case-control study

- 1) Where the evidence for a hypothesis is weak there is a need to have as many sources of information as possible.
- 2) The study would augment the viral work proposed (temporal bone studies).
- 3) By looking for "triggers of reactivation" in cases and controls give an idea of the probability of the "reactivation hypothesis". The temporal bone studies in contrast would give an idea of "residence" also known as the persistent or latent state.

- 4) To look at histories of cold sores between the groups. This is a development of McCormick's (1972) suggestion that differences in cold sore history should be observed between Bell's palsy cases and controls. This examines recrudescence.
- 5.) The need to assess the value of other aetiological factors (than linked with the hypothesis).

1.3.4 The value of a descriptive study

- 1) A community based study would contribute to the understanding of the natural history of Bell's palsy.
- 2) Would give a clearer idea of the incidence with implications for the temporal bone study.
- 3) Would provide a background against which the hypothesis could be discussed.
- 4) Need to repeat Adour's work using a different denominator.

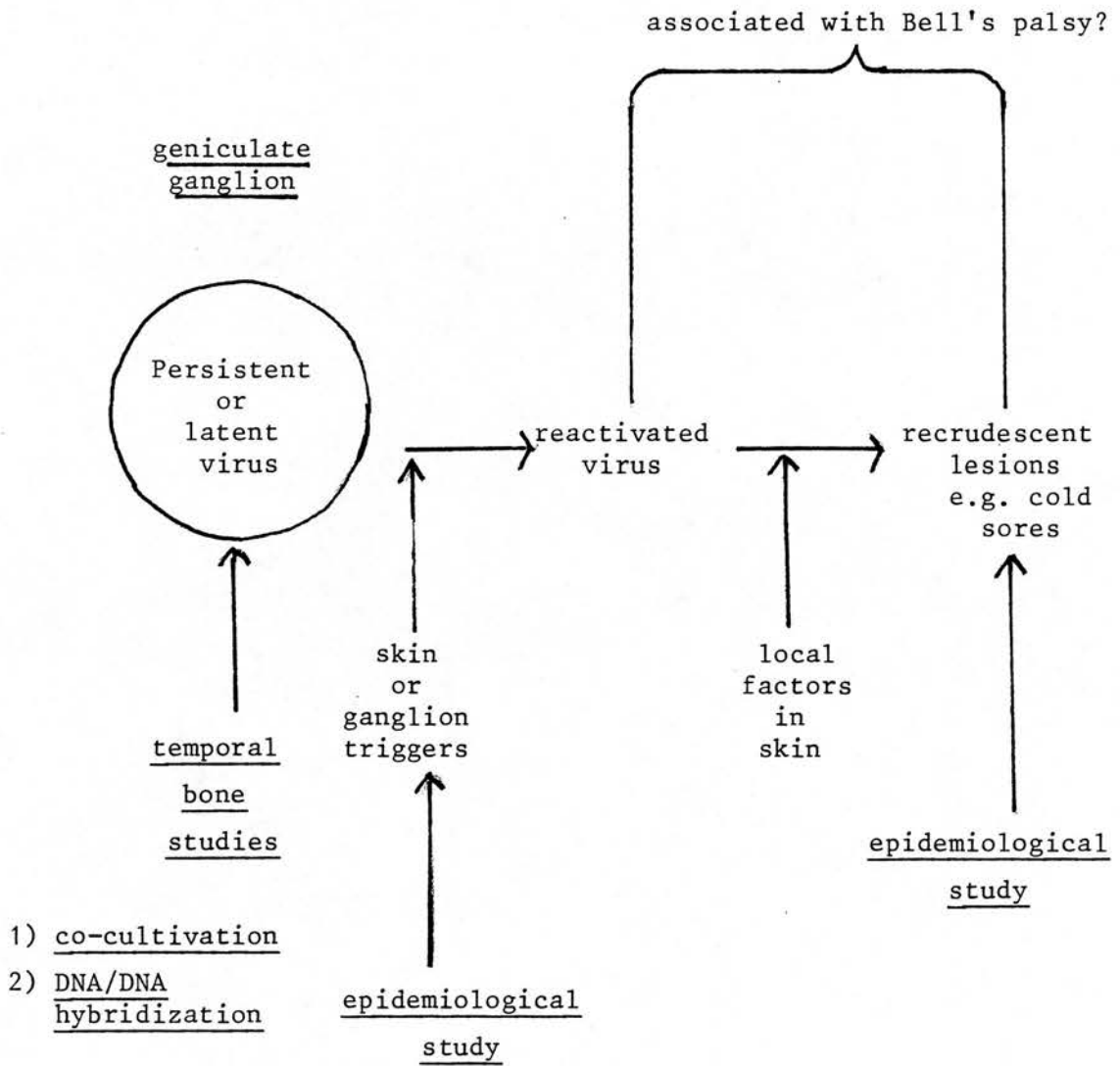
Adour's work also needs to be repeated by an antibody study to see if high (but stationary) antibody levels to HSV exist in Bell's palsy patients - a state observed during HSV reactivations.

1.4 Summary

Existing research is inconclusive as to the cause or causes of Bell's palsy. Whilst appreciating that widely divergent views are held about the aetiology it is the author's observation that in recent years a viral cause has been sought by most researchers. May (1987) writes "accumulating evidence supports a viral inflammatory immune mechanism". Of viral aetiologies the HSV model proposed by McCormick and developed by Adour is arguably the most viable (or less arguably - difficult to disprove). Difficulties in finding methods to confirm or refute this hypothesis have been discussed. Of these the author favours two main areas of enquiry. Firstly a temporal bone study to determine if HSV resides in the geniculate ganglion of the normal (deceased) population (a reasonable assumption of a reactivation hypothesis). Secondly by supporting this work with epidemiological studies in Bell's palsy cases and controls which looks for associations with factors which are known to produce HSV reactivation and recrudescence, and historical differences in HSV exposure.

Fig. 1,1

How aspects of proposed research fit together



The author's own hypothesis is an original development of McCormick's and Adour's ideas, and is used not only in directing the research but also and primarily as a means of making sense out of existing research about Bell's palsy. (see chapter 3).

For a summary of how aspects of the research are related see fig. 1.1 opposite.

CHAPTER 2

The Nature of Bell's Palsy

2.1 Summary Review

The purpose of this chapter is to consider aspects of the clinical and pathological nature of Bell's palsy. The first part describes the clinical features of Bell's palsy. The evidence for the site of the lesion is further discussed first in relation to conduction studies, and secondly in relation-ship to clinical assessment of polyneuropathy in Bell's palsy. Prognosis and outcome complete this section. In the second part the evidence for the site of the lesion is again examined along with curious features of the pathology.

To some extent the contents of this chapter must represent an arbitrary selection from a large topic area, representing fact and speculation. Aspects of the nature of Bell's palsy are covered elsewhere in the thesis particularly under the background to the epidemiological studies.

2.2 Clinical Features

2.2.1 Symptoms in Bell's palsy

Apart from facial weakness these include:- auricular pain and tenderness which may precede the paralysis by several days. The pain may be felt within the ear or over the mastoid and occiput, and occasionally in the jaw and neck, and even over the whole side of the face and neck. About 50% of patients with Bell's palsy complain of pain in the ear or headache. Pain is thought to be of bad prognostic significance by Taverner 1959 and McGovern 1966, but conflicting evidence was found by Park and Watkins 1949 and Jongkees 1973.

Taste to the anterior two-thirds of the tongue is through the chorda tympani branch of the facial nerve. Lesions of the chorda tympani or proximal facial nerve often produce very discrete defects of taste sensation which the patient can localise accurately. About 1/3rd of patients with Bell's palsy have this symptom. (Byl & Adour 1977).

Taste loss may precede the paralysis by days, as may occipital headache. Lacrimation may appear to be increased in Bell's palsy but this is mainly due to mechanical factors. The drooping lower lid impairs

the drainage of tears through the nasolacrimal ducts. This may be tested using Schirmer's test. A dry eye may be the result of a lesion proximal to the greater superficial petrosal nerve. Crocodile tears and gustatory sweating occur in less than 10% of patients with Bell's palsy. Vertigo may be associated with Bell's palsy as studied by Rauchbach (1975). The patient may complain of rotational vertigo or 'dizziness' and spontaneous nystagmus may be noted.

2.2.2 Features of L.M.N. lesions of the face

LMN lesions of the facial nerve are distinguished from UMN lesions clinically by involvement of the frontal belly of occipito frontalis. A useful classification of UMN lesions is found in Mathews and Miller (1975). UMN lesions produce a shock period of flaccidity followed by spasticity of the facial muscles. Loss of the nasolabial fold is often observed. LMN lesions may produce a paralysis or a stimulation of the muscles innervated. The paralysis is usually of sudden onset, with the patient often noticing it on waking. It is often at its worst within 48 hrs and electroneurographic studies show 90-98% degeneration of fibres reached by the 14th day (Fisch 1983).

The motor paralysis usually affects the whole of one side of the face and the severity may be graded. (See fig. 10,9). Facial asymmetry is noted with loss of forehead creases, and the nasolabial fold, and inability to close the eyelids. The corner of the mouth droops and this is more noticeable whilst smiling, and is a problem to the patient whilst eating and drinking.

2.2.3 The somatic sensory function of the facial nerve

This sensory function of the facial nerve is confined to a small area of skin in the external auditory meatus, and neuralgic pains in the ear may be relieved by division of the nervus intermedius (of Wrisberg). This is the region in which Zoster vesicles occur in Ramsay-Hunt syndrome.

2.2.4 Further signs in Bell's palsy

Bell's phenomenon may be observed - named after Sir Charles Bell who described it in 1829. The patient he described had a traumatic facial palsy and was unable to close the eye. An upward rotation of the eyeball was observed; this is in fact a normal movement on closing the eyes.

In some patients when asked to look up, the eyeball goes up higher than on the non-paralysed side. This is Negro's sign and is thought to be an attempt by the ocular and palpebral levators to compensate for the defective contractility of the occipitofrontalis muscle.

When the orbicularis oculi is involved Dupuy-Dutemps sign may be observed which is the gradual opening of the eyelid after the patient has been asked to look downwards and close his/her eyes tightly.

The Bergara-Wartenberg sign or reflex, which is the vibration of orbicularis oculi in normal people when lightly pressed with a finger, may be absent as an early sign of involvement of the temporal and upper zygomatic branches of the facial nerve.

2.2.5 Differential diagnosis

Lower motor neurone paralysis of the face includes a wide differential diagnosis. It may be a symptom of serious intracranial disease, such as a tumour in the cerebello-pontine angle, metastatic deposits, multiple sclerosis or a brainstem infarct. As the facial nerve passes through the temporal bone it may be damaged by fractures or during surgical procedures. It may be produced by otitis media, acoustic neurofibroma, or carcinoma of the middle ear or exhibit the Ramsay Hunt syndrome as a result of Herpes Zoster (although there is some evidence that this latter condition is a brain stem syndrome and nothing to do with geniculate herpes). Extracranial causes include tumours of the parotid gland, trauma or such general conditions as polyneuritis, mononucleosis and sarcoidosis. Of all causes of facial palsy the commonest are injuries of the nerve at various levels, otitis media especially associated with cholesteatoma, and the Ramsay Hunt syndrome.

Headache is most frequently found in LMN facial palsies associated with chronic ear disease and its onset may be of great clinical significance (indicating involvement of the meninges). Neoplasms of the middle ear with dural involvement often give rise to temporal headaches. Acoustic neuromas and posterior fossa tumours produce occipital headaches. Although acoustic neuromas often cause considerable pressure on the facial nerve this seldom gives rise to facial weakness (R.T. Ramsden personal communication).

Viral infections of the CNS may cause a meningo-encephalitis and prodromal symptoms include general malaise and headache. Migrainous type headaches may be associated with transient facial palsies often with paraesthesia of the face (Pearce 1975). Such headaches are usually extremely severe and associated with nausea and vomiting as well as other focal neurological deficits.

Apart from serology and conduction studies few investigations are performed for a straightforward case of Bell's palsy. Time may be used both in a diagnostic and therapeutic sense providing the clinician is satisfied that he or she is not missing any potentially serious or correctable causes.

2.3 Clinical Evidence of Polyneuropathy in Bell's Palsy

Adour (1976) states that other cranial nerves are involved in Bell's palsy. In 40% of patients he noted a vestibular disturbance (8th nerve), 35% had an abnormal gag reflex (9th nerve) and in 25% facial numbness was noted (5th nerve).

In 1978 Adour records the incidence of 5th nerve and 9th involvement in 48 consecutive patients. 19% had 5th nerve only, 19% 9th nerve only and 29% had both.

Bell's palsy may not affect exclusively the 7th cranial nerve but may also be part of a widespread cranial and even peripheral neuropathy (Adour 1975, Djupesland 1977, Lundgren 1977, Adour 1978, May 1978, Sandstedt 1981, Nieuwmeyer 1982, Odkvist 1982, Abdel-Baki 1988). Adour argues that hyperacusis is not due to stapedial muscle involvement but is a feature of recruitment and is due to cochlear or retrocochlear lesions, which he found in 10% of patients with Bell's palsy (Adour 1978). Pietersen (1982) has noted phonophobia in 12% of cases. Abnormal ENG's have also been recorded in Bell's palsy.

In conclusion the evidence that Bell's palsy can sometimes be part of a polyneuropathy seems without doubt. The strength of the association is difficult to assess however. Selected patients might be expected to have an artificially high frequency of polyneuropathy, and this is discussed further in the results section (p.158).

2.4 The Evidence of Conduction Studies in Bell's Palsy for the Site of the Lesion

Broadly speaking these studies are indicative of multifocal and sub-clinical disease in Bell's palsy. Adour in 1975 demonstrated in his patients that 50-75% had pathological nerve conduction on the opposite, uninvolved side. Although clinical simultaneous bilateral palsies are very uncommon (about 1% in most series).

2.4.1 Trigeminal evoked potential

Hanner in 1986 showed that 47% of patients with Bell's palsy had an abnormal response suggesting a lesion somewhere along the trigeminal nerve and tracts into the sensory cortex.

An abnormal blink reflex (described by Kugelberg 1952, Kimura 1983) was found in 60% of patients. In 2 patients in Hanner's study a TEP was pathological but the B.R. was normal suggesting a more central trigeminal affection and may demonstrate multifocal lesions. Of the 60% with abnormal blink reflexes 24% had a solitary brain stem lesion (R_1 & R_2 components generated in the brain stem) whereas 36% had trigeminal involvement as part of a cranial polyneuropathy and or with a brain stem lesion.

Vahlne (1985) produced corroborative evidence stating that of 28 patients with Bell's palsy who were extensively neurologically examined 57% showed evidence of brain stem impairment or cranial polyneuropathy. The most frequent abnormality was an impaired contralateral corneal reflex.

There is a close anatomical relationship between the facial tract and the trigeminal nuclei and there may be coordinating functions between the facial and trigeminal neuronal systems (Hanner 1986). In Hanner's study 14 out of 17 with a complete palsy had trigeminal dysfunction but only 6 of 13 with an incomplete palsy had a corresponding trigeminal dysfunction. Facial pain which is arguably a bad prognostic criterion in Bell's palsy also demonstrates the interaction of trigeminal and facial neuronal systems.

2.4.2 Electromyography

Takahashi (1985) discovered preparalytic conditions of the facial nerve by evoked electromyography. 2 patients with herpes zoster oticus who had developed vesicles but with no apparent paralysis showed abnormal EMG responses (low amplitude, short duration). The interesting conclusions from this study are that sub-clinical or preparalytic pathology exists with herpes oticus and by inference with other speculated causes of Bell's palsy e.g. HSV.

2.5 Assessing Prognosis and Outcome

A detailed method has not been used in this study to assess facial nerve function but rather the paralysis has been graded either complete or incomplete. Pietersen (1982) showed that of 1,071 patients from Copenhagen collected over a 15 year period, complete paralysis was noted in 69% of patients and incomplete in 31% of patients.

The chances of complete remission decreased with each decade with 90% recovering at 0-14 yrs, 85.6% at 15-29, 76% at 30-44, 61% at 45-59 and 37% over 60 years.

Pietersen used the following detailed grades to assess outcome:-

- 0 No associated movements.
- I Slight palsy and contracture less than 1mm just visible without associated movements.
- II Moderate palsy with clearly visible contracture and associated movements.
- III Severe palsy with disfiguring palsy and associated movements.
- IV Complete atonic facial palsy without contracture and associated movement (no cases seen).

The final outcome in his series was as follows:-

- 0 71%
- I 13%
- II 12%
- III 4%

From Pietersen's study it appears that complete remission occurs in 30%, at 1 month after the onset of the palsy, is slow from the 3rd week to the 3rd month and then tails off to 6 months as recovery

approaches 100%. Most patients with incomplete paresis obtain remission within 1 month.

Pietersen found that idiopathic and pregnancy groups have the best prognosis. 75% without sequelae (other groups zoster, diabetes, polyneuritis and neonates) have sequelae in 75%.

Diabetic patients have been noted to have a more severe nerve injury and a less favourable outcome. (Adour et al 74 - 2 refs). Adour calculates the extra risk to be 3X greater of developing degeneration (diabetic v. nondiabetic). Younger and older diabetics appeared to be at equal risk.

Pain is a symptom in 62% of patients with Bell's palsy. When the pain is limited to the occipital (retro-auricular) region it has no prognostic significance. However when the pain is in the ear canal, face or neck the patients are at higher risk of denervation. The time delay in starting therapy in Bell's palsy also significantly alters the prognosis (Taverner 1971).

2.6 The Pathological Nature of Bell's Palsy

The pathology is reviewed because the findings represent 'hard evidence' in an area where all aetiological hypotheses should have a sure base. Furthermore the pathological findings themselves are both central and difficult to explain in the aetiological controversy around Bell's palsy.

2.6.1 Surgical appearances of the nerve

The macroscopic appearances of the nerve in Bell's palsy is based predominantly on the operative findings of surgeons performing decompression operations. Hilger (1949) states "that the usual finding upon surgical exposure is oedema of the nerve with the trunk most tightly constricted by the nerve sheath at its point of issuance from the stylomastoid foramen". Cawthorne's findings are in agreement, he also noted swelling of the nerve above the stylomastoid foramen. At the site of constriction haemorrhagic streaks were noted running longitudinally.

Kettel (1947) noted that the nerve in Bell's palsy was swollen in 28 cases out of 50 operations. At operation (in patients within 2 months of onset of the palsy) "there was always a strong swelling, mostly with a fierce redness of the nerve sheath". In older cases there was less congestion and the redness had disappeared. In some long standing cases marked atrophy of the nerve was described as "looking like a silk thread".

Macroscopic findings in recent years of swelling of the facial nerve have focused on the suprageniculate part of the nerve. Fisch (1983) states that at decompression operations damming of axoplasm can be seen at the entrance to the fallopian canal where the diameter is narrowest in 19 out of 20 cases. His findings have aroused considerable interest. O'Donoghue (1985) also reported a case of Bell's palsy where these same appearances were noted.

2.6.2 Descriptive pathology in Bell's palsy

Histological examination of the nerve in Bell's palsy has been undertaken very few times, since it is a non-fatal condition and biopsy impairs function.

Minkowski (1891) noted in a 27 year old man who died 8 weeks after the onset of a facial palsy normal appearances of the facial nerve from the nucleus to the geniculate ganglion. In the most external part of the Fallopian canal however there was a very marked degeneration. The axon cylinders were mostly intact but the medullary sheaths were greatly swollen. He noted at the point of departure of the chorda tympani the greatest part of the fibres were degenerated.

Dejerine and Theorai (1897) found changes similar to Minkowski with no evidence of inflammation.

Alexander (1902) noted round cell perivascular infiltration along the endoneurium as far proximal as the geniculate ganglion. He states there was no evidence of inflammation in the perineurium and endosteum. No mention is made of vessel engorgement.

Mirallié (1906) observed globules of myelin in various sizes peripherally with absence of axon cylinders.

André Thomas (1907) found evidence of peripheral Wallerian degeneration and stated "Il n'existe nulle part de perineurite ni d'endoneurite". A finding which still holds true today and which should therefore preclude the use of the term 'neuritis' when applied to Bell's palsy. Mills (1910) also found no evidence of inflammation in an 80 year old patient.

In more recent times Fowler (1963) reports the histology of a patient dying with a palsy of 14 days duration. The sections were performed serially on the decalcified temporal bone and mounted in collodium.

"The left seventh nerve was most unusual. Its entire course contained or was surrounded by dilated and engorged veins and venules. Degeneration of the myelin sheath and axis cylinders was more or less apparent in the entire intratemporal course of the nerve. There were small fresh intraneural haemorrhages here and there on both sides of the stylomastoid foramen and all along the fallopian canal. The arteries and arterioles looked normal ... Most striking and unexpected were the fresh haemorrhages in and around the facial nerve in the internal acoustic meatus between the region of the normal vestibular ganglion (Scarpa's) and the narrow bony channel of the porus acousticus proximal to the geniculate ganglion. Here there were several quite large and separate intraneural haemorrhages as well as general infiltration of the nerve with red blood cells. No evidence of inflammation of any kind was found".

The author supposes the haemorrhages noted in the suprageniculate part of the nerve to be due to the widespread vascular disease found in the patient and not part of the disease process. Since he does not cite evidence of other endoneural haemorrhages this interpretation remains hypothetical.

Fowler continues "Some of the ganglion cells of the geniculate ganglion stained more palely than the normal side and some of them look pyknotic. If disease was present in the ganglion it was neither impressive nor conclusive". The stump of the facial nerve as it entered the brain stem was also examined and found to be normal.

Jongkees (1972) noted swelling of the facial nerve at the genu with a swollen chorda tympani nerve. This latter was biopsied. Prof. Deelman noted "no sign of inflammation can be found anywhere. Nor is there increase in the number of cells. The nerve fibres are distinctly at least locally degenerated". Jongkees concludes from the macroscopic and microscopic evidence that it is quite acceptable to make the assumption of an acute vascular disturbance followed by degeneration.

Proctor, Cargill and Proud (1976) reported on the histology of a patient dying with Bell's palsy on the 10th day - the patient dying of a cardiac arrest on the operating table, the surgeons's intention being to decompress the nerve.

They note phagocytosis of myelin by macrophages, beginning of axonal swelling, increased cellularity due to lymphocytic infiltration, and a moderate proliferation of Schwann cells and fibroblasts. These changes are evident throughout the entire course of the facial nerve from the internal auditory meatus to the stylomastoid foramen. No information was obtained from the nerve at brain stem level as only the intratemporal course of the nerve was examined. Adour (1978) contests Proctor's findings by stating that Bell's palsy "may represent inflammation and demyelination rather than ischemic compression". Proctor notes "acute inflammatory changes in the nerve trunk with subsequent swelling and compression of the vascular channels in the fallopian canal". The use of the word "subsequent" by Proctor appears as an unsupported rationalization in this context.

Proctor also notes "markedly dilated blood vessels accompanying the swollen chorda tympani nerve" but there was "absence of evidence of vascular occlusion".

Fisch (1983) in a study involving 6 biopsies of the greater superficial petrosal nerve noted lymphocyte infiltration in 3 patients. In the 3 geniculate ganglia studied the appearance was normal and there was no evidence of degeneration in the unmyelinated fibres whereas 5 of the 6 biopsies showed moderate to severe degeneration of the myelinated fibres.

The most recent post mortem report in the literature is O'Donoghue's (1985). In contrast to most earlier studies large numbers of lymphocytes were noted infiltrating the geniculate ganglion. Michaels the pathologist involved writes (1987), that the specimen showed "a geniculate ganglionitis possibly of viral origin with secondary periostitis of the adjacent bony canal". The histopathology of Bell's palsy is further reviewed by Liston (1989).

2.6.3 Discussion

The pathology of Bell's palsy is markedly understudied due to obvious difficulties in obtaining specimens.

Most studies have failed to show an acute inflammatory response which is a significant finding in a condition of abrupt onset. Proctor, O'Donoghue and Mills all noted a small round cell infiltration however. Vascular dilation particularly of the venules with congestion and haemorrhage has been more consistently noted.

Is the pathology thus outlined consistent with a viral aetiology? Unfortunately most virus infections do not produce diagnostic lesions. They may produce cell necrosis, cell proliferation or no lesion at all in the case of latency. "Neuronophagia" is seen in polio C.N.S. infections and phagocytosis of neuronal debris by macrophages is indeed noted in Bell's palsy. The lack of a heavy small round-cell infiltration and meningeal perivascular cuffing is against certain types of viral infection (e.g. polio). It is interesting that Schwann cell proliferation has been noted but not so far, gliosis.

Electron microscopic studies of the geniculate ganglion for viral inclusion particles have been inconclusive (Palva 1978).

The pathology supports a vascular process as part of the disease mechanism but whether it is primary or secondary is not clear. What is clear is that there is no evidence of thrombosis or vessel occlusion in the vasa nervorum. Curiously inflammatory cells and lymphocytes are not present in most cases.

The anatomical site of the lesion in Bell's palsy is also a subject of controversy. The evidence that the brain stem is involved comes principally from evoked potential studies. The evidence of other nerve involvement comes principally from further nerve conduction studies and clinical examination. In contrast the localised nature of the lesion is emphasized by operative findings - "the macroscopic appearance of the nerve". This is supplemented by Fisch's work (1983) on intraoperative electroneurography showing a conduction block near the entrance to the Fallopian canal. These findings are also supported by the pathological reports of the intratemporal portion of the facial nerve in Bell's palsy cases.

The evidence appears sufficiently strong to support the idea that Bell's palsy is a localised disease of the 7th nerve and also quite often part of a generalized disease process. It is quite possible to interpret the evidence in conflicting ways. Firstly that it supports the notion of multiple aetiological agents in Bell's palsy - making it a type of syndrome. Or alternatively that like atheroma for example, localised disease may exist as part of a generalized process, in a more florid form as a result of anatomical, mechanical, and other factors. The author inclines to the economy of the second view, with the narrow entrance to the Fallopian canal making "strangulation" and ischaemia more likely. Such factors are discussed in more detail in the next chapter.

CHAPTER 3

The Aetiology of Bell's Palsy - Hypothetical Considerations

3.1 Introduction

The purpose of this chapter is to discuss an original hypothesis for a pathomechanism in Bell's palsy. The first hypothesis is a development of the hypothesis proposed by McCormick and Adour that Bell's palsy is due to reactivation of HSV but at a defined site, in the geniculate ganglion¹; as a result of which further events are proposed to happen². This "extension" or wholly new hypothesis is drawn from a wide area of existing research.

The value of including it within the context of the thesis is primarily as a means of attempting a fuller or more cogent explanation of the curious facts of Bell's palsy. That is, it is an attempt to incorporate a wider body of research into the explanation of observed clinical events. Events which in the author's opinion are not adequately explained by an HSV reactivation hypothesis alone.

However because of the dangers inherent in attempting to link hypotheses the author has formulated his own research in the logical order of testing the first unproven hypothesis first, and the scheme for this is outlined in the next chapter under aims and objectives. Testing the second part of the hypothesis requires further research and this is discussed in the final chapter. Thus in terms of a research base this chapter stands alone from the rest of the thesis, but provides it with a wider framework for interpretation.

A Mechanism in Bells Palsy

Due deference should be given to the difficulty of finding a solution to the cause or causes of Bell's palsy when considering the enormity of the historical debate. Although the linked hypotheses here discussed, present many difficulties they present 'a substrate' from which the 'analytical appetite' may feed with appropriate scepticism. However to continue with the metaphor, excessive scepticism in the search for meaning can result in 'anorexia', just as too little may result in 'obesity'. In the aetiological debate around Bell's palsy rival theorists often hold

on to a flimsy certainty whilst being dismissive of alternative accounts. It is hoped that the linked-hypotheses here outlined by maintaining some of the strengths of opposing arguments, and by taking cognisance of some of the 'curiosities' of Bell's palsy achieves a way of reconciling the evidence, rather than simply being syncretic statements of belief.

3.2 Hypotheses

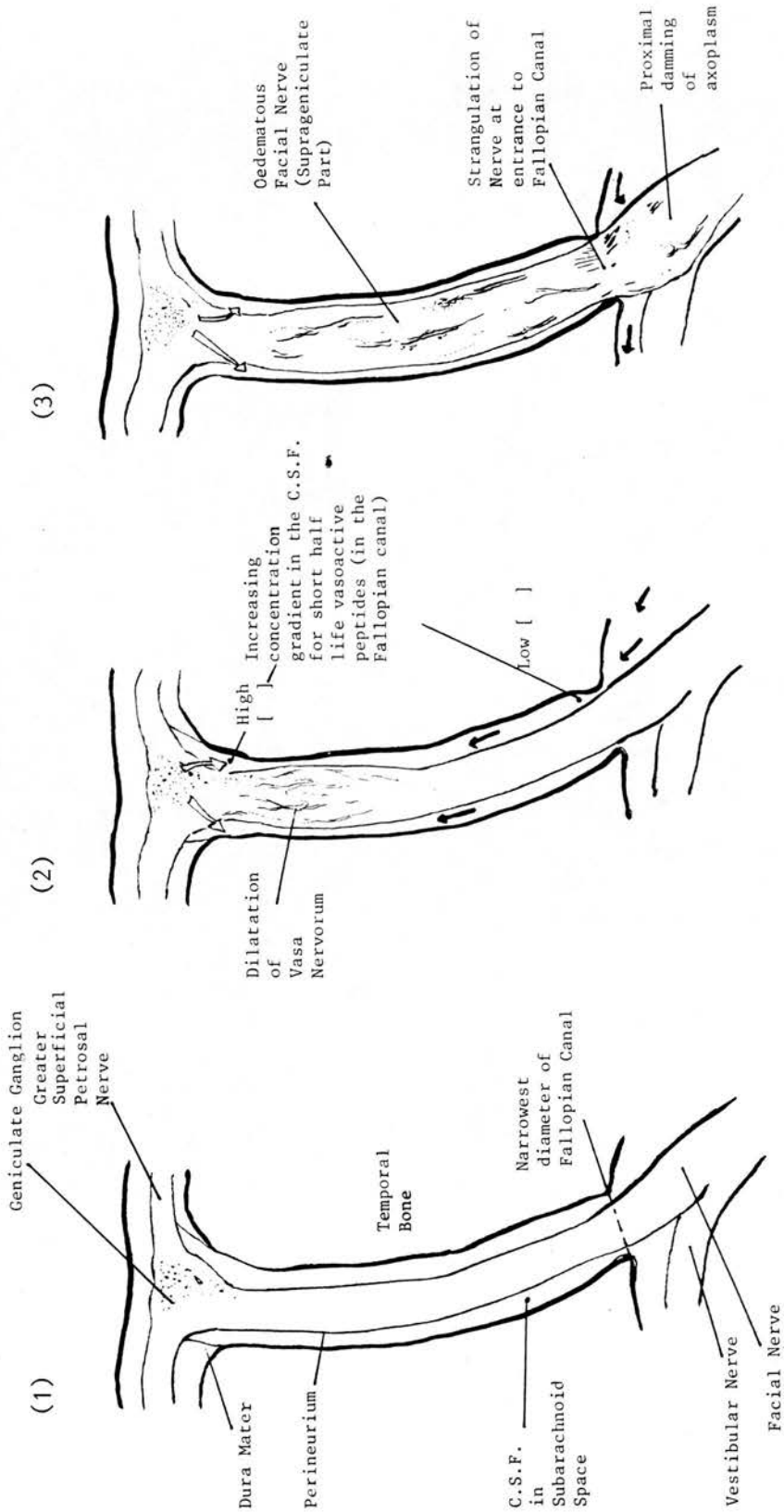
1) That a viral agent resident in the geniculate ganglion, most probably H.S.V., undergoes reactivation in response to a biological stimulus - "stress".

2) This results in a production of interferon and opioid peptides which have a local vasoactive effect. This effect is most marked where the nerve is bathed in CSF (also where these peptides have a longer half-life). The concentration of peptides is biologically variable. In those individuals particularly sensitive to opioid peptides this may lead to loss of local autoregulation, and where anatomical factors impede venous return in the swollen nerve - such as at the narrow entrance to the Fallopian canal more severe damage to the nerve (rather than dysfunction) may be expected. The damage to the nerve will be variable depending on the degree of vasodilation produced and its duration. This mechanism would be compatible with a conduction block in most instances with degeneration only occurring when the nerve is "strangulated" - using the hernia analogy by the narrow entrance of the Fallopian canal (see Figs.3,1, 3,2). It has been shown in cats that increasing the pressure inside the nerve is detrimental to the function of the nerve (Devreise 1972)

The linked-hypotheses are multifactorial incorporating viral, vascular and constitutional elements. It is in essence an abnormal local "physiological " response induced by a virus i.e. an exaggeration of the "stress" response. Since this virus-induced disorder of physiology is the basic "event" of the mechanism, antibody responses to the virus may not be significant as observed with HSV neural reactivations.

Interferon and opioid peptides may be produced by physiological as well as diverse stimuli (Bocci 1985). These stimuli include other infectious agents than HSV. Also glucocorticosteroids inhibit the production of interferon and its actions, pyrexia stimulates it (Isaacs 1962).

Figure 3.1: Schematic Diagram of Hypothesis - A Mechanism for Damage to the Suprageniculate Part of the Facial Nerve?

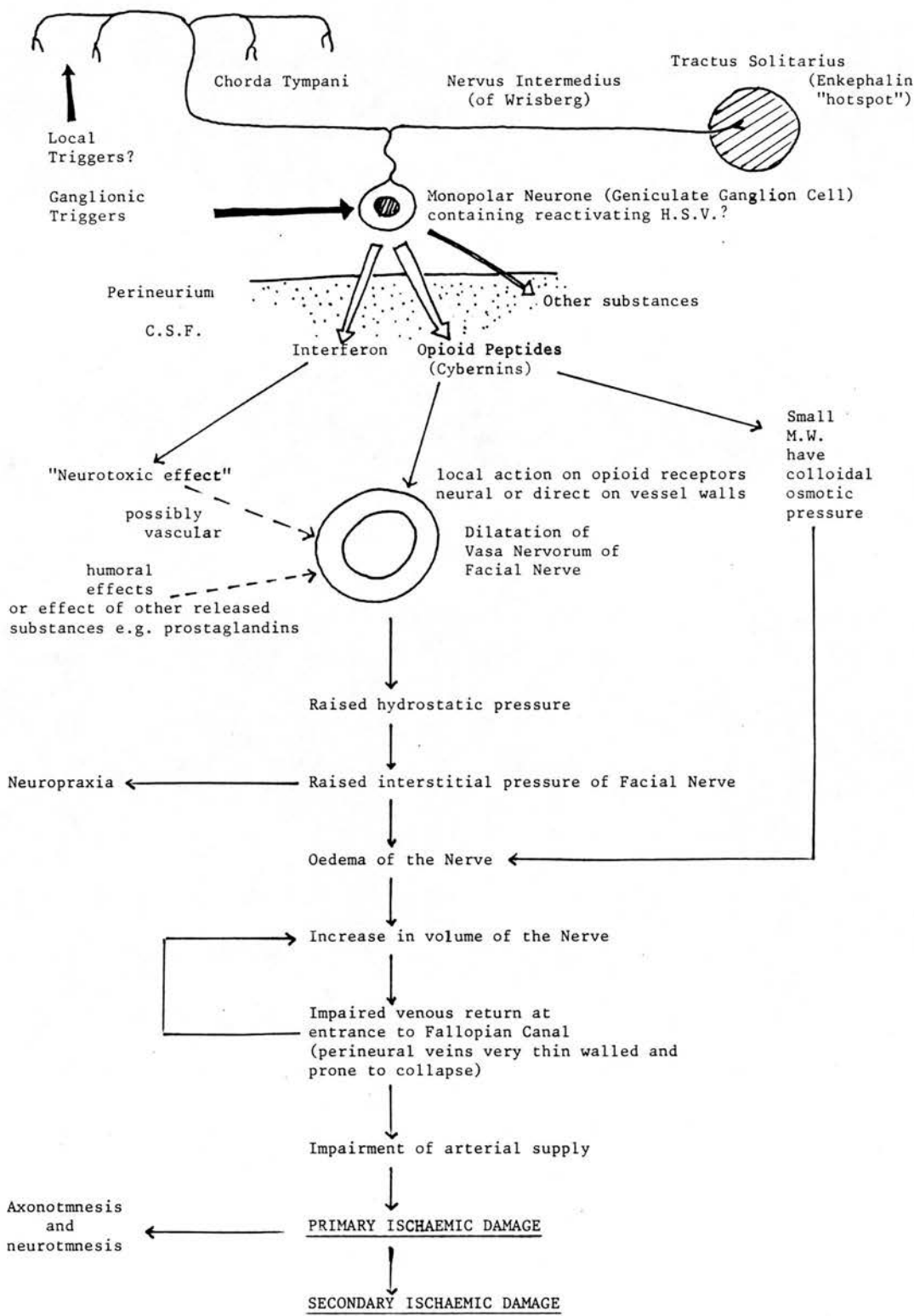


Release of vasoactive opioid
Peptides/interferon

Flow of C.S.F.

Figure 3.2: Hypothesis in algorithmic form

Taste receptors in tongue and palate



Thus the second part of the hypothesis could be "triggered" separately and be considered independent of the suggested first mechanism. The main direction of research has followed amassing more evidence for the HSV reactivation hypothesis on the grounds that some definite mechanism for inducing the interferon/opioid system is needed for the second part to be a viable proposition and that on the basis of research already discussed in relation to the aetiology of Bell's palsy the HSV reactivation hypothesis seems most worthy of further scientific enquiry; and preceding pyrexia is also of some interest.

3.3 Viral Factors in Bell's Palsy

It is known that at least in some instances Bell's palsy may be associated with a viral infection. Furthermore Fisch has made the interesting observation that the level of facial nerve injury is suprageniculate in over 90% of cases. This also corresponds with the part of the nerve that is bathed in CSF (see fig. 3.1) and does not correspond with the central/peripheral myelin junction. Fisch theorizes (1979) that this may be due to the actions of concentrated viral "toxins" on the nerve root. The idea seems an attractive one apart from two faults. Firstly there is no evidence that CSF is concentrated around nerve roots, and secondly and more significantly viruses do not produce "toxins" as such (typically this is a property of bacteria). Fisch thus gives important information about the site, and his ideas about a local "toxin" deserve development where this is possible.

A virus in a geniculate ganglion neurone might be expected to act by increasing cell production of viral protein and/or host cell proteins, including interferon. It is not unreasonable to suppose that an infected ganglion cell might produce excessive quantities of neurotransmitter. Although little is known of the neurotransmitters of primary afferent neurones, substance P, dynorphin, and opioid-like immunoreactivity have all been found. (North & Egan 1983, Sweetnam et al. 1982, Boticelli 1981, Jessell 1979). It is also known that the tractus solitarius (fig. 3,2) is an autoradiographic 'hot spot' for the enkephalins (Kuhar & Uhl 1979, Miller & Cuatrecasas 1979). As a working assumption it will be supposed that a percentage of the geniculate ganglion neurones normally produce opioid peptides. The fact that this group of transmitters requires mRNA for synthesis unlike

most other types of neurotransmitter renders it particularly compatible with a viral mechanism.

There is no doubt that interferon is produced by cells infected with numerous viral agents including H.S.V. Elevated levels of γ and α interferon have been observed in the CSF as an early response in HSV encephalitis (Meyer 1986, Frei 1988, Lebon 1988). It has also been observed that serum interferon levels are raised in Bell's palsy patients. There are no studies to date of CSF interferon levels in Bell's palsy.

Further interesting work comes from Blalock (1984) who noted that when lymphocytes were stimulated with mitogen both interferon and opioid peptides were produced simultaneously. He concluded that there is considerable interrelatedness between the immune and neuroendocrine systems, and this is supported by earlier work (Blalock 1980, 1981). Furthermore he also noted antigenic and structural relatedness between γ endorphin and human leukocyte interferon. This intriguing relationship between interferon and opioid peptides is worthy of careful consideration when extrapolating to the ganglionic "reactivation" scenario.

It is speculated that either geniculate ganglion cells or in some cases lymphocytes are the source of interferon and opioid peptides in the pathogenesis of Bell's palsy. Lymphocytes have been shown to be ubiquitously present in trigeminal ganglia (Ball 1982). According to Hill (1983) "whether such immune cells are present as a response to reactivation of latency, or whether they are concerned with maintenance of latency, remains to be established".

3.4 Interferon as a "Neurotoxin"

It is known that neuropathies occur in patients taking high dose interferon therapy, even when using highly purified forms (Nethersell et al. 1984). The authors of this paper also noted that 3 patients with painful bone metastases required less analgesia on interferon therapy. This observation seems to be in keeping with the mechanism of interferon induced CNS toxicity as discussed by Bottomley (1985). She argues that the work of Blalock (1980, 1981) suggests that "potent endorphin like opiate activity of α -interferon may be related to CNS toxicities experienced during therapy in humans".

Disorders of taste and smell have also occurred in patients taking purified interferons (Inigmarsson 1979, Mattson 1983, Gutterman 1982, Laszlo 1983, Sarna 1983). That interferon has been shown to produce a neurotoxicity affecting the taste pathways is of considerable relevance when interpreting the clinical picture of Bell's palsy. Firstly because a viral mechanism is considered a strong possibility; secondly because elevated interferon levels have been observed, and thirdly because a high proportion of Bell's palsies have an associated taste disturbance.

Numbness and tingling as part of a peripheral neuropathy are noted both in Bell's palsy patients and in those on high dose interferon therapy. Mattson (1983) noted slowing of motor and sensory conduction velocities recorded by electromyography in patients receiving intravenous interferon. Fever and fatigue noted in patients on interferon are also observed in some patients prior to developing a Bell's palsy

All this raises the intriguing possibility that the clinical picture of Bell's palsy may be due in part to a neurotoxic effect of interferon or a related mediator (opioid peptide). There is broad support for this idea from Mattson's work; she states that there is the "possibility that endogenous IFN plays a role in the pathogenesis of virus-induced encephalopathy and neuropathy". Since intravenously administered interferon does not cross the blood-brain barrier its effects could well be mediated by endorphins. However if the geniculate ganglion were the site of "infection" in Bell's palsy - then this should be considered part of the peripheral nervous system. The argument would then be that both interferon and endorphins could be released into the C.S.F. or have neurological effects on local vasculature.

A high local concentration of interferon and opioid peptides might thus be found in the ganglion cells and the C.S.F. bathing the supra-geniculate part of the facial nerve as a consequence of HSV reactivation. This could produce a neurotoxicity of the chorda tympani nerve and a disorder of taste sensation. Where intravenous interferon is given however negligible concentrations of interferon in the CSF might be expected and a lower incidence of neurotoxicity.

How interferon produces a neurotoxicity may be further considered. Most of the neuropathies observed have been reversible when the dose was

decreased or stopped. This squares with a vascular mechanism of nerve "damage" (amongst other possibilities). Nothing is known of the effect of interferon on the cerebral circulation although α interferon produces a marked flare response when injected intradermally. This was observed in 5 patients by the author whom he skin-tested prior to their being treated for laryngeal papilloma (see appendix 4c). If it could be demonstrated that this effect were mediated by a cell of neuroectodermal origin this would greatly increase the salience of these observations in support of the hypothesis. (The merkel cell may be a mediator of opioid induced skin flushing. Do similar cells exist in ganglia and/or the CNS and behave in broadly similar ways?).

A further interesting study showed paradoxical effects of interferon on reactivation of oral infection with herpes simplex virus after microvascular decompression for trigeminal neuralgia (Ho et al. 1984). This study suggests interferon may actually precipitate or accentuate herpes reactivation. If this is the case then this would result in a rewording of the hypothesis such that interferon and opioid peptides would be produced by some process prior to reactivation which when this occurs further amplifies this process.

3.5 Opioid Peptides and Vascular Responsiveness

The physiology of opioid peptides is extremely complex with ever increasing amounts known since their discovery in 1975 (Kosterlitz 1975, Hughes 1975, 1977, Goldstein 1976) and their physiology and pharmacology are reviewed by Lord 1977, Guillemin 1978, Spence 1984, Thompson 1984 and Miller 1979. They are characterised by a short half life in plasma, usually less than a minute, but this is prolonged significantly in C.S.F. (by a factor of 3 or 4 for the enkephalins). Because of this short half-life they are thought to act as local messengers or cybernins, and their complex pharmacokinetics makes it difficult to assess local activity e.g. in the C.S.F. around the facial nerve from blood tests. The term opioid peptide is used generically throughout the thesis and it is accepted that this is an imprecise way of relating information. It is serendipitous for the hypothesis therefore that from the little that is known about the effects of these peptides on the cerebral circulation most of the evidence is consistent in indicating loss of vessel wall tone, irrespective of the opioid peptide studied. (Hanko 1978, Partridge 1981, Baskin 1981, Dashwood 1978, Koskinen 1983, Moore 1979).

In Hanko's study on cat pial artery blood vessels, dilation was produced in a dose dependant manner by enkephalins and morphine in vitro. This vasodilation was blocked by naloxone suggesting the presence of opiate receptors on the vessel walls. Increasing the dose of leu-enkephalin from 2 pmol/ml to 11 pmol/ml was sufficient to cause 50% dilation of the vessel wall. These concentrations indicate high activity at very low concentrations (similar to the vascular action of interferon). This paper is limited in being an in-vitro study, which alters the compliance of the vessel wall (this usually decreases) compared to in-vivo studies.

Knoll in 1976 showed an effect of enkephalins on the ear artery of the rabbit by acting on a specific presynaptic neuronal receptor. The receptors involved in such studies if specific would be μ receptors for morphine or δ for leu-enkephalin. However dynorphin 'the most likely opioid peptide' to be found in afferent ganglia would act on K receptors.

Further experimental work by Koskinen and Bill 1983 has shown that morphine can increase cerebral blood flow in some parts of the rabbit brain, (e.g. by up to 30% - the hippocampus). Interestingly this is also a site of predilection of HSV within the CNS (Esiri 1982) and the taste and smell pathways are typically involved in interferon neurotoxicity (Mattson 1983). Are these merely coincidental observations or is there a viral-cellular connection?

Facial flushing induced by chlorpropamide and alcohol can be blocked by naloxone suggesting a role for enkephalins in arterial dilation in humans (Leslie 1978, 1979, Barnett 1980, Johnston 1984) but contested by Kobberling 1980. Although the plasma I.R. enkephalin level rises this is not thought to be the mechanism, but rather by an action of chlorpropamide and alcohol on autonomic ganglia. Could 'intracranial flushing' also be occurring? Facial flushing is known to occur in the distribution of branches of the external carotid (Leslie and Pyke 1978). The external carotid artery does supply some intracranial areas including areas supplied by the stylomastoid artery, (a branch of the posterior auricular artery) and the petrosal artery and artery to the geniculate ganglion - (the latter being branches of the middle meningeal artery). The artery to the geniculate ganglion divides and one branch runs proximally along the facial nerve to the porus acousticus supplying the labyrinthine section as do branches from the anterior inferior cerebellar artery,

a branch of the internal carotid (Nager 1953, Ogawa 1982, Proctor 1982) Thus it is quite conceivable from the anatomy that flushing around the supra-geniculate part of the facial nerve occurs during this process (C.P.A.F) and that like facial flushing some individuals are more sensitive to this process. The conclusion would be that this group are "constitutionally sensitive" for the development of a Bell's palsy. This sensitivity is also much commoner in non-insulin dependent diabetics.

As a development of the C.P.A.F observations as a model for Bell's palsy, further comments can be made with respect to the hypothesis. Namely that to be a valid mechanism in Bell's palsy the vasodilation in Bell's palsy would have to be related to "centrally controlled pathways involving autonomic ganglia" - such as the cranial parasympathetic outflow and ganglia. In this respect neurones in the geniculate ganglion directly innervating the local cerebral circulation might provide the link whereby such vasodilation might be produced. It is known that the parasympathetic outflow of the 7th nerve passing through the geniculate ganglion is the main parasympathetic innervation of the cerebral blood vessels. A viral reactivation in cells of this pathway might result in excess production of neurotransmitters (opioid peptides) which would be inhibitory to fibres maintaining the tone of the vessel wall - usually noradrenergic fibres (sympathetic). A sustained vasodilation might well be produced for longer than an effect where neurotransmitters were acting directly on the vessel wall. With such a mechanism sympathectomy would be ill-advised.

Many other substances normally produced by cells are capable of vasodilation. Prostaglandins might be locally increased by an action of interferon. Mora (1984) showed that indomethacin reduced the side effects of intrathecal interferon and concluded that interferon induced prostaglandin formation (other than E_2) in brain tissue. Some prostaglandins vasodilate and others vasoconstrict. Although the role of Prostaglandin E_2 in recrudescence HSV (cold sores) seems now established, the possible role of these arachidonic acid derivatives in Bell's palsy aetiology remains unknown. Substance P might vasodilate or constrict, depending on the circumstances. Tullo in 1983 using experimental herpes simplex keratitis in mice noted that levels of substance P dropped quicker and for a longer period in inoculated mice than mice controls (which only had scarification of the cornea). Tullo suggests this may be due

to destruction of nerve endings by virus or by some inflammatory mediator. Considering HSV is rapidly transported to the trigeminal ganglion, Tullo speculated that damage to the nerve cell body may also have occurred. It is thus unlikely that substance P is a significant mediator of a vascular response in HSV infections. However opioid peptides if increased locally (ganglion or cornea) would inhibit substance P release, thus providing a fourth possible explanation of Tullo's findings. Given the complexity of cellular pathways it is impossible to exclude effects produced by these and other substances. It is the author's opinion that a stronger case can however be made for interferon and opioid peptides as 'primary mediators'. Other reasons for considering opioid peptides particularly salient are that there is a peculiar anatomical relationship of the nerve swelling to the geniculate ganglion suggesting a "toxin" which is more active or prolonged on blood vessels bathed in CSF than those which are not. Furthermore ACTH in high doses is a worse treatment than prednisolone in comparably high doses for Bell's palsy (Taverner 1971). "The evidence for this is statistically unassailable" according to Groves (1979). On careful consideration of why this should be apart from slight differences Na^+ concentration may make to receptor binding, is the reasonable conclusion that ACTH which has opioid activity, is in some way involved in the disease process.

Further arguments come from epidemiological considerations of different types of stress in the aetiology of Bell's palsy. These arguments are discussed in more detail in chapter 11. Can stress be considered to be acting in so simple a way as producing a reactivation of HSV, or are the possible effects of stress more complex as the outlined hypothesis might suggest?

3.6 Difficulties with the Overall Hypothesis

The main argument against the hypothesis is that it is 'too general', and therefore unlikely to be the cause of a relatively rare condition.

It is too general on account of HSV being ubiquitous affecting almost 100% of the population. Primary infection with the virus occurs principally in 0-5yr olds and 15-20yr olds whereas Bell's palsy is commoner in 6-12yr olds and 20-35yr olds (Fisch 1979). Furthermore "stress" which is difficult to quantify, is also commonplace in society

and its effects are diverse on cellular pathways. All cells are capable of just about any response. The key question is, are the responses likely to be significant in a pathophysiological sense?

Further difficulties with the present hypothesis are that it is difficult to either prove or disprove. Little is known of the neurotransmitters present in the geniculate ganglion and whether they are as vasoactive in humans as they appear to be in animals. Systemic levels of opioids are by no means indicative of what might be happening locally to the facial nerve.

A further problem with the HSV reactivation model acting by triggering a vascular response is the fact that HSV produces demyelination at several sites in the C.N.S. where the 'strangulation model' can less readily be evoked. So general factors would be needed for the vascular mechanism proposed to produce nerve damage elsewhere. These would have to include:-

- 1) good blood supply to nerve of "sensitive" vessels
- 2) thin walled veins such as the cerebral veins prone to collapse (leGros Clark W.E. 1965)
- 3) no lymphatic drainage (no lymphatics in the skull or vertebral canals)
- 4) high Basal Metabolic Rate
- 5) proximity to cells which can produce interferon and opioid peptide (vasodilators) and their release from those cells by a virus "infection" or other trigger
- 6) anatomical factors likely to cause compression e.g. a narrow entrance to the Fallopian canal.

In summary it would appear that the hypothesis is almost too general to entertain seriously. However there are forceful features and curiosities of the clinical condition which defy explanation except by such a hypothesis and furthermore it is consistent with the way viruses and in particular HSV are likely to act.

3.7 Summary of Supporting Features of Hypotheses Parts (1) and (2)

3.7.1. Primarily supporting part (1)

- 1) Animal models e.g. mouse ear, tongue, rabbit-eye of HSV induced demyelination in C.N.S.
- 2) Finding of HSV in afferent (autonomic) ganglia in animals and man e.g. geniculate in animals but geniculate in man?
- 3) Antibody studies incriminating HSV in Bell's palsy.
- 4) Epidemiological studies of factors common to Bell's palsy and cold sores e.g. upper respiratory infection, stress and menstruation.

3.7.2 Support for linking hypotheses parts (1) and (2)

- 1) If a viral agent is involved in the aetiology of Bell's palsy particularly HSV then activation of the interferon/opioid system does not involve a quantum leap of credibility.

3.7.3 Primarily supporting part (2)

- 1) Elevated interferon levels have been observed in Bell's palsy patients. High interferon levels have been observed to produce neuropathies.
- 2) The site of the lesion as observed by Fisch is difficult to account for by traditional explanations and is indeed a sticking-point for most theories. However opioid peptides would be expected to act more forcefully on the CNS side of the ganglion than the infra-geniculate part, and perhaps explain why Fisch has found a ratio of nerve damage of 19:1, suprageniculate:infrageniculate.
- 3) Association of Bell's palsy with N.I.D.D. Some studies show a strong association between Bell's palsy and diabetes. It has been proposed that N.I.D.D. may be due to a genetically determined state of increased opioid sensitivity (about 1/3rd of N.I.D.D.'s are opioid sensitive compared to 1/10th of the general population). The chlorpropamide-alcohol flushing model is a particularly interesting one in relation to the aetiology of Bell's palsy and of considerable relevance to the hypothesis. In effect the mechanism could explain the association of the two conditions.
- 4) The polyneuropathy observed in Bell's palsy patients and abnormal electroneurological tests could be explained partly by increased endogenous interferon production.

- 5) The treatment of Bell's palsy has brought to light a curious finding. Taverner's 1971 study showed that ACTH was worse treatment than a comparable dose of prednisolone. This perhaps suggests that ACTH or opioid receptors are sometimes involved in the disease process.
- 6) Sudden onset; and also a general lack of inflammatory cells in pathology studies suggest a vascular event as the main part of the mechanism. Both interferon and opioid peptides can produce a marked vasodilation in low doses.

3.8 Summary Statement

This multifactorial linked-hypothesis resolves some of the viral/vascular traditional hypothesis conflicts in as much as it is predominantly a vascular response, and not an "acute inflammation", occurring in response to a viral initiated event, which in sensitive individuals produces sufficient nerve dysfunction or damage to be noticeable to them.

CHAPTER 4

Proposed Research: Aims and Objectives

4.1 Abstract of Hypothesis

The hypothesis of how facial nerve injury might come about in Bell's palsy can be divided into two parts:-

- a) Bell's palsy is due to a reactivation of HSV in the geniculate ganglion.
- b) During this process, neurotransmitters (opioid peptides) and interferon are produced. These cause local vasodilation and damage to the suprageniculate part of the facial nerve.

The research proposed is directed towards testing the first part (a) of the hypothesis. Part (b) of the hypothesis provides a further possible explanation of how Bell's palsy might come about when considering diverse sources of information from different research disciplines.

The testing of this part of the hypothesis is beyond the scope of this thesis. It is however relevant to the work of the thesis when trying to understand if factors supposedly acting by triggering "reactivation" e.g. menstruation and "stress" actually do act in this way. The second part is an original mechanism suggested by the author, but drawn from the research work of others, which it is hoped adds interest to the discussion, and against which results may be interpreted. In keeping with the general principle known as Occam's Razor* the thesis will aim to test the first part of the hypothesis only.

4.2 The Aims of the Research:-

- 1) To examine for the presence of HSV in the geniculate ganglia of a proportion of the general population.
- 2) To test, by clinical method, evidence which appears to link HSV infection, particularly recrudescence and reactivation, with Bell's palsy; and also examine for associations, other factors of suggested aetiological relevance.

* Entia non sunt multiplicanda praeter necessitatem (entities ought not to be multiplied except from necessity).
William of Ockham (d.1349)

- 3) To contribute to knowledge about the incidence and nature of Bell's palsy. As seen in less strongly selected, more community based patients than hospital studies.

4.3 The Objectives of the Research:-

Objectives concerned with achieving the first aim

- 1) To remove the temporal bones of patients dying of natural causes. To examine the geniculate ganglia for the presence of HSV:-
 - a) by isolation of HSV - a cocultivation study
 - b) by examining for the presence of HSV genome - a DNA/DNA hybridization study.
- 2) To examine the trigeminal ganglia removed from the same cadavers as a means of assessing the methods outlined above. Only one attempt has been recorded in the literature using cocultivation on geniculate ganglia and none for DNA/DNA hybridization, whereas the literature using trigeminal material is more extensive.

Objectives concerned with the second aim

- 3) To use a case-control study to examine for differences between cases and controls by means of match-pair analysis. The exposure to factors studied would be:-
 - a) history of cold sores (recrudescence)
 - b) history of HSV exposure (primary infection and other recrudescence lesions)
 - c) factors known to be associated with reactivation/recrudescence including humoral factors
 - d) other aetiological factors.
- 4) To do an antibody study to assess if "high antibody levels to HSV" are found in Bell's palsy cases. Where possible to use paired antisera to see if these levels are stationary.

Objective concerned with the third aim

- 5) To describe the clinical features of Bell's palsy by means of history and examination in a case finding study based in general practice over a 1-year period. To make inferences about the incidence and clinical nature of Bell's palsy.

4.4 Discussion of the Aims and Objectives

Aims 1 and 2 are hypothesis testing (see chapter 3 for further details of hypothesis). The third aim is an expansion or development of the second aim beyond hypothesis testing and standing in its own right.

The first aim sets out to test the belief -

"That HSV resident (persistent or latent) in the geniculate ganglion, reactivates to produce a Bell's palsy".

Implicit in the first part of this statement is the assumption that HSV resides in the geniculate ganglia of a proportion of the general population. From which a proportion could reactivate and from these a proportion could develop a Bell's palsy.

To be a valid hypothesis HSV must be found to be actually present in a proportion of cadaveric geniculate ganglia removed from people dying of natural causes. Given that a reliable and sensitive method of identification is being used, and that an adequate sized sample is taken.

Because it was predicted that the first aim would provide only limited evidence for the hypothesis, the second aim was developed. "To use clinical method to explore the HSV reactivation hypothesis". The first aim being limited in being "detection" rather than recrudescence or reactivation orientated. The limitations of the first aim in hypothesis testing and the need for clinical supplementation are best understood when considering possible outcomes in terms of imagining frequencies of detection in the ganglia for the general population.

- 1) Higher identification rate in ganglia of the general population than predicted from epidemiological, clinical and virological studies. This would imply that the hypothesis is either not valid or that factors not considered in part (1) of the hypothesis are important.
- 2) Identification rate in ganglia of the general population commensurate with epidemiological, clinical and virological predictions. This would be compatible with a valid hypothesis but not constitute proof of a causal relationship.
- 3) Failure to isolate HSV from the ganglia of the general population. This would falsify the hypothesis.

These conclusions particularly in 1 and 2 are difficult to maintain because at best the "carriage rate in the general population" can only be very crudely estimated or intelligently guessed. Based on the hypothesis (part I) and an incidence of Bell's palsy of 20 per 100,000 per year and taking a cumulative incidence over 70 years. A correction for under reporting of 2 and a correction for subclinical disease of 2 and a correction for being present and reactivating of 0.5 to 1 would give a predicted "carriage rate" of 5 to 10 per 100 ganglia studied. A further serious problem with such "predictions" is the debate about the frequency of reactivation and the validity of the analogous model to Bell's palsy - the cold sore lesion. The latter involves the 5th rather than 7th nerve and the skin rather than the ganglion.

The second aim is a further indirect method of examining the hypothesis but by clinical method rather than a laboratory approach; and examining recrudescence and reactivation rather than persistence of HSV. The information yielded should thus be complementary. A limitation of the second aim is that it cannot provide causal evidence, but rather it is the strength of the associations e.g. factors associated with recrudescence of HSV in Bell's palsy and controls which will be mainly examined. A clinical approach alone is likely also only to present weak evidence with which to assess the hypothesis. The problems with the more traditional clinical "proofs" e.g. biopsy and antibody studies have already been discussed in the introductory chapter.

The second and third aims are also linked in relation to hypothesis testing and the third aim should yield community study incidence information central to a proper evaluation of the hypothesis.

In summary the first and second aims are primarily hypothesis testing using different methods of scientific enquiry which are feasible and valid, to a problem which is complex and difficult. The third aim whilst also of relevance to the hypothesis is mainly directed to clinical description of a condition in an area largely uncharted by studies from this country.

The stated aims are sequenced from the more specific to the more general third aim in the historical order in which they were formulated.

The title of the thesis emphasizes the general nature of the condition under study and the importance the author attaches to an overview of his own work, and that of other researchers. It is quite possible that the problem of how Bell's palsies come about remains so simply because the boundary of the problem does not coincide with the boundaries of individual disciplines necessary for understanding.

PART I OF RESEARCH

The Temporal Bone Studies

CHAPTER 5

2 studies which attempt to isolate or identify HSV from cadaveric (human) geniculate ganglia using trigeminal ganglia as controls -

Materials and Methods

STUDY 1 - Cocultivation study5.1 Materials Used (1)5.1.1 Study population

Patients who died of natural causes between Feb. 1985 and June 1985 at Manchester Royal Infirmary. 42 temporal bones were removed yielding 42 geniculate ganglia and 42 trigeminal ganglia from the same cadavers were used as controls).

5.1.2 Materials used for obtaining ganglia (see materials DNA hybridization study). The ganglia were collected in:-

labelled 2ml plastic sterile containers containing viral transport medium:-

1ml aliquot

Hanks B.S.S. 85%

foetal calf serum 10%

4.4% NaHCO₃ 2.5%

Crystamycin

{ Pen.V200 units

{ Streptomycin 200 µg/ml

fungizone 5 µgm/ml.

5.1.3 Co-cultivation materials

Calibrated Gilson micropipettes (France)

Sterile petridishes (Sterilin Ltd. London)

Swann Morton scalpel size 10 blades

Glass-slides

70% alcohol

25 ml plastic cell culture flasks (Falcon U.K. Ltd.)

Eagles Minimal Essential Medium (Flow Lab. Irving Scotland)

20% foetal calf serum (Flowlab. Irving Scotland)

2 mmol glutamine (Sigma Chemicals U.K. Ltd.)
100 μ /ml phosphate buffer (B.D.H., U.K.)
100 μ ml streptomycin 100 u/ml penicillin (Flowlab. Irving Scotland)
Incubator at 37°C and 5% CO₂ (Flowlab. Irving Scotland)
Source of Vero cells (Flowlab. Irving Scotland)
Cell counter/haemocytometer (B.T. Ltd. U.K.)
Binocular microscope x 10 x 20 power (Olympus U.K. Ltd.)

Co-cultivation study

5.2 Methods (1)

The method used for removal of ganglia was similar to that used in the DNA/DNA hybridization study. Except that all ganglia once extracted were placed in viral transport medium containing fungizone.

The specimens were taken to the viral laboratory where they were finely minced by use of a sterile scalpel blade and cleaned forceps into approximately 1mm³ fragments. The tissue from each ganglion was divided in half and placed in 25ml flasks. Each flask was then overlaid with cell growth medium. This contained 100ml of Eagles Minimal Essential medium with 4ml (4.4%) sodium bicarbonate with pink indicator, 1% crystamycin (100 u/ml penicillin and 100 μ ml streptomycin) and 10ml (10%) foetal calf serum. 25ml flasks (appropriate labelled) were then incubated at 37°C in a 5% CO₂ atmosphere. The growth medium was removed every seven days by pipette and carefully replaced. The cultures were monitored three times a week for cytopathic effect. Passage of the supernatant to vero cells was performed weekly or more frequently for observation of cytopathic effect.

The above methods were taken from Barringer 1973 and Warren 1977 who obtained isolation rates of HSV of 85% and 60% respectively for trigeminal ganglia. For a review of the literature see p. 72. Because of problems with the methodology satisfactory results were not obtained. This is further discussed in Chapter 7.

Table 2: Ganglionic Specimens Obtained at Post-mortem

Patient No.	Age	Sex	Cause(s) of Death	Time of post-mortem hours after death	Ganglia and side	
					Vth nerve	VIIth nerve
1	79	M	C.V.A.	12 hrs	R+L	R+L
2	86	F	C.V.A.	15 hrs	R+L	R+L
3	44	M	M.I.	12 hrs	R+L	R+L
4	65	F	Pulmonary embolus	20 hrs	R+L	R+L
5	61	M	Acute asthma	10 hrs	R+L	R+L
6	80	M	Prostatic neoplasia	38 hrs	R+L	R+L
7	78	F	Cerebral thrombosis/atheroma	56 hrs	R+L	R+L
8	89	F	Cerebral thrombosis	31 hrs	R+L	R+L
9	67	M	M.I. coronary atheroma	14 hrs	R+L	R+L
10	86	M	M.I. hypertensive H.D.	80 hrs	R+L	R+L
11	80	M	Heart failure - LVF	47 hrs	R+L	R+L
12	68	F	Heart failure - mitral stenosis	30 hrs	R+L	R+L
13	65	F	CCF coronary atheroma	20 hrs	R+L	R+L
14	62	M	Pneumonia	44 hrs	R+L	R+L
15	56	M	Pseudomonas septicaemia/acute myeloid leukaemia	72 hrs	R+L	R+L
16	57	M	Sup. mesenteric vein thrombosis	38 hrs	R+L	R+L
17	70	F	Pulmonary embolus	36 hrs	R+L	R+L
18	68	M	M.I. hypertension	32 hrs	R+L	R+L
19	62	F	Carcinomatosis, ca colon.	51 hrs	R+L	R+L
20	87	M	Heart failure	48 hrs	R+L	R+L

Key: MI-Myocardial infarction; HD-Heart disease; CVA-Cerebro vascular accident; CCF-Congestive cardiac failure



STUDY 2

DNA/DNA Hybridization Study - attempts to identify HSV genome in human post mortem material

5.3 Materials (2)

5.3.1 Study population

The temporal bones (paired) and trigeminal ganglia (paired) were removed from 20 patients who died in Manchester Royal Infirmary between December 1985 and January 1986 and in July and August of 1986.

The patients died of natural causes and no coroners deaths were included. A history of Bell's palsy was not recorded in any of the patients' hospital records. One patient was noted to have non-insulin dependent diabetes, and the same patient was also noted to have congenital syphilis.

The group thus represents a selection of hospital deaths and is not necessarily representative of deaths in the general population (see table opposite).

Temporal bones were removed when the following criteria were fulfilled.

- 1) Permission from relatives had been obtained.
- 2) The mortuary staff had available time.
- 3) The death was not a coroners death.
- 4) There was no evidence of meningitis.
- 5) The death had occurred recently (limit of 72 hours).

From these specimens, 40 geniculate ganglia were obtained and 40 trigeminal ganglia were removed from the same patients to serve as controls.

5.3.2 Materials used for obtaining ganglia

Labelled pathology specimen containers for transport to dissecting room.
(- for temporal bones)

Cotton wool pledgets

70% alcohol

Toothed dissecting forceps - short

Swann-Morton scalpel and blades sizes 10, 12

Labelled 2ml plastic sterile containers (for trigeminal ganglia)
 Circular bone-saw
 Zeiss binocular operating microscope
 Temporal bone holder
 Saline-irrigation device
 Electric drill
 Selection of drill heads - different burr sizes including diamond burrs
 Drill cleaning equipment (antiseptic and brush)
 Down's instrument cleaning trough
 Swann Morton scalpel and blades sizes 10, 15
 Fine toothed forceps
 Down's periosteal elevators (selection)
 Beale's elevator (Down's)
 Weiss microscissors
 Down's bone curettes - various sizes
 Clothing items:-
 Surgeons gloves/apron/face mask/gown

5.3.3 Probing materials

Liquid nitrogen storage container at -20°C (Union Carbide U.K.)

Extraction of DNA from ganglia

Calibrated pipettes	
Eppendorf tubes	Sarstedt U.K. Ltd.
1mm ethylene diamine tetraacetic acid E.D.T.A.	B.D.H.
0.15m sodium chloride	"
Acid washed sand	"
P.E. buffer - (10mMTris, 1mM EDTA Ph 7.9)	"
Slim glass rods	
20 μ l 10% sodium dodecylsulphate	"
Proteinase K stock solution	Sigma
Incubator 55°C	L.T.E. Ltd. U.K.
400 μ l phenol/chloroform	B.D.H.
Centrifuge	M.S.E. U.K.
Chloroform/isoamyl alcohol (24:1)	B.D.H.
40 μ l of 3M sodium acetate	B.D.H.
800 μ l absolute ethanol	James Burrough Ltd.
70% ethanol	"
Vacuum system	

U.V. Spectrophotometer	Pye Unicam Ltd.
Silicon currettes	Pye Unicam U.K.

DNA probes

Plasmid containing Tk probe for HSV, supplied Dr. E. Littler, Christie Hospital, Manchester, designated - PE Tk₁.

Whole plasmid M.W. 9.57 kbp.

Tk gene was contained in a 3.6 kbp fragment of HSV genome - Bam HIQ fragment - inserted at Bam HI site within the plasmid.

E. coli HB101.

Hybridization assay

BRL Hybridot apparatus	BRL Ltd. Paisley Scotland
0.45 μ nitrocellulose membranes	Scleicher & Schull Andersson & Co., East Molesey, Surrey.
Distilled water	
20x SSC (3M sodium chloride, 0.3M sodium citrate)	B.D.H.
0.3N sodium hydroxide	B.D.H.
2M ammonium acetate	B.D.H.
Incubator 80°C, 65°C	L.T.E.
Non-fat dry milk	Cadbury's Ltd.
Blotto solution 0.25%	
0.1% S.D.S.	Sigma Chemical Co.
0.1 x SSC	

Autoradiography - film/apparatus	Kodak U.K.
Kodak X-omat S film	"
Kodak X-omatic S intensifying screens	"

Bam HI DNA restriction enzyme	Amersham U.K.
Gel electrophoresis apparatus	Pharmacia

Controls

Positive - DNA extracts from Vero cells
infected HSV-1 strain SC-16

Negative - DNA extracts from inoculated Vero cells
from 3T3 cells known to be TK deficient

Radiolabelling 32P - d CTP (30 μ ci)	Amersham U.K.
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5.4 Methods (2)

5.4.1 Removal of ganglia

The study had been given approval by the Regional Ethical Committee. Permission for post mortem was obtained by the doctor responsible for the care of the deceased patient. A standard form in use at Manchester Royal Infirmary was signed by the next of kin. This gives permission for tissue to be removed for research purposes (see appendix 4b).

Enquiries were made on a daily basis about arrangements for post mortems. The author attended the post mortem where appropriate cases had been found and permission obtained. The calvarium and brain were removed by the mortuary technician.

The trigeminal ganglia were dissected out from each side before the temporal bones were removed; thus preventing possible damage to these ganglia by the bone-saw. Wearing gown, apron, surgeons cap, mask and gloves the author first cleaned the area at the apex of the temporal bone and the dura covering the cavernous sinus, and also the area around the entrance to the cavum trigeminale using cotton wool soaked in 70% alcohol. Using cleaned toothed dissecting forceps and scalpel with a sterile size 10 blade the semilunar ganglion was removed from the cavum trigeminale to incorporate several millimetres of the three main branches of the nerve, and also a corresponding rim of tissue proximal to the ganglion. The ganglia were placed directly into labelled plastic 2ml sterile containers (recording name of patient, age, and side).

The temporal bone specimens were removed in pairs by the mortuary technician, using a bone-saw, under the author's directions. A quadrilateral block of temporal bone was removed of approximate dimensions 4cm long, 2cm high and of width 2cm anteriorly and 3cm posteriorly (figs 5,1-3). Laterally the section approximated the middle ear cleft. The anterior edge lay just posterior to the cavum trigeminale and 2cm in front of the internal acoustic meatus. The posterior edge lay 2cm posterior to the internal acoustic meatus. Inferiorly the section was approximately $\frac{1}{2}$ cm below the internal acoustic meatus. During removal the landmark of the superior arcuate eminence was carefully noted and preserved; (the geniculate ganglion lying close antero-inferiorly). This method of removal, rather than removal of the whole temporal bone preserved the

Fig. 5,1 Petrous Temporal Bone Specimen
Quadrilateral Block — Showing Porus Acousticus

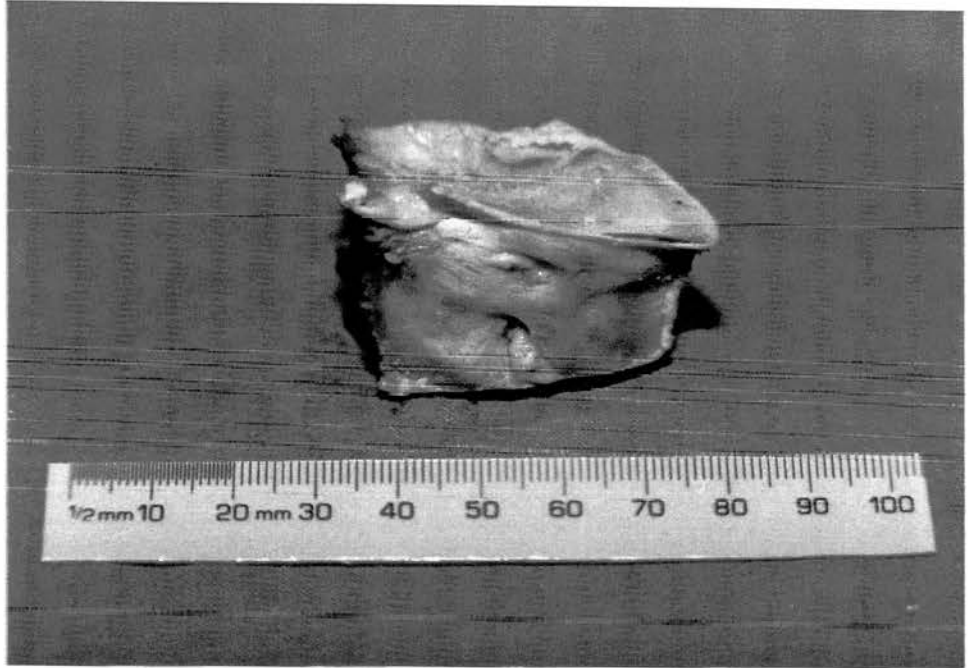


Fig. 5,2 Superior Aspect with drilling commenced in
region of geniculate fossa

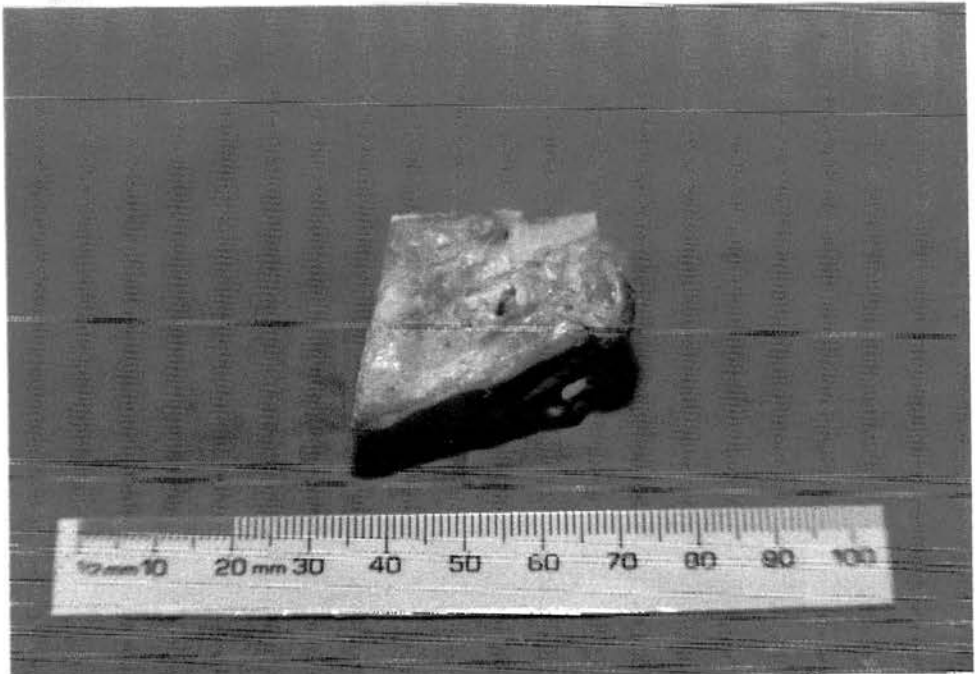
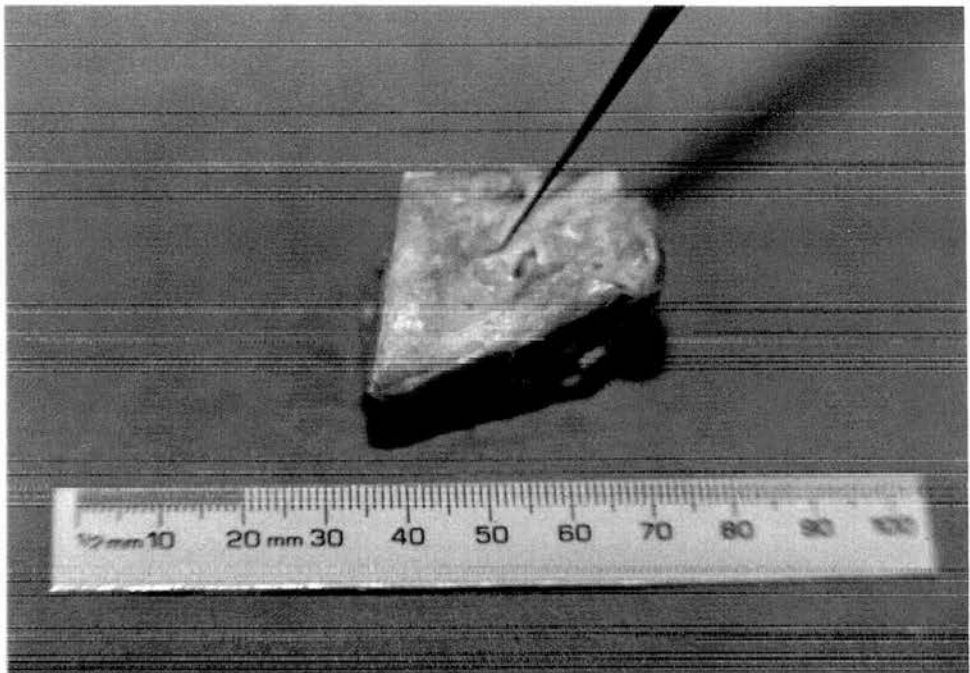


Fig. 5,3 Elevator in contact with geniculate ganglion
in its fossa



outer appearance of the auricular region, and especially since bilateral specimens were obtained was in consideration of the relatives supposed wishes.

The specimens were placed in labelled pathology containers and taken to the temporal-bone room for further dissection. The instruments used had been cleaned using a brush, and soaked in chlorhexidine in spirit for 24 hrs. Sterile scalpel blades were used, and the instruments for right and left sides kept separate to avoid any tissue transfer to the opposite side container.

Gowned as previously described the author first orientated the temporal bone. An incision with a scalpel was made 2cm anteriorly to the superior arcuate eminence, and using a periosteal elevator the periosteum was removed carefully to demonstrate the greater superficial petrosal nerve disappearing into its foramen. Having cleared the bone of periosteum recourse was made to the landmarks of the superior arcuate eminence, the greater superficial petrosal nerve and the internal acoustic meatus before drilling. The geniculate ganglion was usually to be found a few millimetres anterolateral to the arcuate eminence and drilling was commenced in this area. The facial nerve was exposed in the horizontal portion as it ran along the fallopian canal to the geniculate ganglion. This 3-5mm length of nerve appeared curvilinear and ended in the geniculate fossa. (As the nerve approaches the fossa it rests on the intervestibulocochlear groove and the cupula). Drilling superior to the ganglion was through petrosal cortex (which stretches from the arch of the superior semicircular canal towards the cupula of the cochlea). This area was variably pneumatized (by cells of the superior pre-labyrinthine tract). The geniculate ganglion was identified in its quadrilateral fossa of approximate dimensions 2 x 2 x 3 mm. The descending horizontal portion of the facial nerve was identified anterosuperiorly to the tympanum, in front of the cochleariform process. (Posteriorly the geniculate ganglion is related to the anterior wall of the vestibule from which it is separated by 2-3mm of compact bone).

The ganglion could be gently teased out of its fossa using fine toothed forceps allowing the intermediate nerve of Wrisberg to be more readily identified - running in the facial canal. Bone curettes were used near the ganglion to reduce tissue damage from drilling. The facial nerve was elevated by gentle traction and divided several

millimetres proximal to the ganglion with microscissors. It is known that ganglionic cells may extend proximally up the nerve for several millimetres beyond the ganglionic 'swelling'. The greater superficial petrosal nerve was divided close to the ganglion as was the descending portion of the facial nerve.

A Zeiss operating microscope x6 magnification was used to facilitate the drilling and the dissection of the geniculate ganglion, but it was not necessary in all the dissections.

The dimensions of the trigeminal ganglion removed were 2 x 4 x 8mm and the geniculate ganglion 2 x 2 x 3 mm. The trigeminal ganglion yielding considerably more D.N.A.

The dissection of the geniculate ganglion was done consecutive to removal of the trigeminal ganglion. The number of hours after death the post-mortem was performed is included in table 2. The average time spent removing geniculate ganglia was approximately 15 minutes per side. All specimens were labelled and stored after dissection in liquid nitrogen.

5.4.2 Extraction of DNA from ganglia

Tissue samples were removed from liquid nitrogen and placed in a 1-5ml Eppendorf tube. 400µl of 10mM Tris pH 8.0 and 1mM ethylene diamine tetraacetic acid (EDTA), 0.15M sodium chloride were added to the tube together with a small amount of acid washed sand. The tissue was ground using a slim grassrod. 20µl of 10% sodium dodecyl sulphate was added to give a final concentration of 0.5%. 5µl of 20mg/ml proteinase to stock solution was added to give a final concentration of 250µg/ml. The Eppendorf tube was sealed and incubated at 55°C for 3 hrs.

The contents were then treated by addition of 400µl phenol/chloroform mixture which was thoroughly mixed and then spun for 1 minute at 15,000 r.p.m. to separate the aqueous and organic phases. The supernatant was retained and extracted with chloroform/isoamyl alcohol, in a ratio of 24:1, to remove any traces of phenol residue. After further spinning the supernatant was transferred to a clean Eppendorf tube. To this were added 40µl of 3M sodium acetate with thorough mixing and 800µl

of absolute ethanol. The samples were then left at room temperature for 10 minutes for DNA precipitation to occur.

The tubes were subsequently spun at 15,000 r.p.m. for 20 minutes and the supernatant carefully removed and discarded. The pellet was washed with cold 70% ethanol to remove salts, and then dried under vacuum for 5-10 minutes. The pellet of nucleic acid was dissolved in 50 μ l of 10mM Tris/1mM EDTA at pH 7.5. Nucleic acid extracts were stored at -20°C until required.

Assays of the DNA concentrations were performed on each sample by standard spectrophotometric methods i.e. by reading the optical density at 260nm and 280nm against a control blank silicon curette. The ratio of $O.D_{260} : O.D_{280}$ should be 1.8:1. The concentration of DNA was calculated on the basis of a DNA solution containing 50 μ g/ml DNA giving an $O.D_{260}$ equal to 1.

5.4.3 DNA probes

The plasmid carrying the thymidine kinase (T.K.) probe for HSV, was supplied by Dr. E. Littler of the Holt Radium Institute, Manchester (Christie's Hospital), and was designated pETK1. The whole plasmid molecular weight was 9.57 kbp and the TK gene was contained in a 3.6kbp fragment of the HSV genome (Bam H1Q fragment) inserted at the Bam H1 site within the plasmid.

Plasmids were transfected into E. coli HB 101, amplified, purified and the HSV insert recovered using standard procedures (Maniatis T., 1982). All cloned DNA probes were stored in TE buffer (10mM Tris, 1mM EDTA, pH 7.9) at -20°C.

5.4.4 Hybridization assays

All tissue samples were initially examined by dot-blot hybridization (Hayes P.C. 1989) using a B.R.L. Hybridot apparatus. 0.45 μ nitrocellulose membranes were pre-soaked in distilled water and equilibrated in 20 x 5.5C (3M sodium chloride, 0.3M sodium citrate).

Patient DNA (2-5 μ g) was rendered single-stranded by denaturing for 10 minutes with 0.3N sodium hydroxide at room temperature and samples were then chilled and diluted with an equal volume of cold 2M ammonium

acetate and applied to walls of the Hybridot apparatus. After binding all walls were washed with 100 μ l of 20 x SSC and the filters were air-dried, and baked at 80°C for 2hrs. Filters were prehybridized using a non-fat dry milk (Blotto) technique (Johnson D.A. 1984) for 24 hrs at 65°C. Following this filters were tagged with radio-active probe (vide infra) which had been rendered single-stranded by boiling. DNA/DNA hybridization was performed at 65°C overnight in the same Blotto solution.

Filters were washed for two half hour periods in 0.25% Blotto, 2 x 55C and 0.1% SDS at room temperature followed by two thirty-minute high stringency washes in 0.1 x 55C and 0.1% SDS at 65°C (T_m -17°C). After drying the filters were put to film and autoradiography carried out at -70°C. Using Kodak X-omat S film and Kodak X-omatic S intensifying screens results were obtained in 16-24 hrs.

Further investigations of the ganglion extracts were performed using Southern transfer analysis (Southern E.M. 1975) following digestion of the cellular DNA with the restriction enzyme Bam H1.

Positive control included in all the above comprised DNA extracts from Vero cells infected with HSV1 (Strain SC-16). Negative control material comprised DNA extracted from uninoculated Vero cells and from 3T3 cells which were known to be TK deficient.

5.4.5 Radio-labelling of probe DNA

Cloned excised 3.6 bhp insert DNA was rendered single stranded by boiling and labelled with 32p-dCTP in-vitro using random oligo-nucleotide primers (Feinberg 1983). 50ng of DNA was incubated with 30 μ Ci of labelled nucleotide yielding probe DNA with specific activities of $2-5 \times 10^9$ c.p.m/ μ g DNA.

CHAPTER 6 - RESULTS

6.1 Cocultivation Study (1)

The results were invalidated because of problems with the methodology. See p. 75.

6.2 DNA/DNA Hybridization Study (II)

Initial investigations were all performed on 5th nerve DNA extracts which had been undertaken by Dr E. Littler at the Molecular Biology Laboratories, Christie Hospital.

The initial probe used (for autoradiographs 6,1 to 6,5 and fig. 6,9) was a 3.6 kbp segment of the HSV genome, the Bam H1 (Q fragment) which contains the sequence of the thymidine kinase gene (T.K.) together with flanking sequences. The probe had been oligonucleotide labelled to a high specific activity with ^{32}P - approximately $2-5 \times 10^9$ c/p.m./ gm DNA.

The amount of DNA obtained after extraction of the 5th nerve ganglionic tissue varied from 20 gm - 290 gm in total. Initial investigations were undertaken by dot-blot assays. Each sample was loaded at between 2 and 7.5 gm of DNA total.

The results are shown in Table 3 and Autoradiograph 1 (fig. 6,1).

Table (3): Dot-blot analysis of 5th nerve ganglion extracts

POSITIVE AFTER 24 hrs (Strong positive)	POSITIVE AFTER 168 hrs (Weak positive)	NEGATIVE	NOT TESTED
2R, 3R, 4R, 5R 6R, 8R, 10R, 11R 12R, 15R, 18L, 20L	1R, 1L, 2L, 3L 5L, 7L, 8L, 9L 10L, 11L, 12L, 13R 13L, 14R, 14L, 15L 16L, 17L, 18R, 20R	4L, 6L, 7R, 19R	9R, 16R, 19L

These specimens were extracted by Dr. E. Littler, Paterson Laboratories, and losses were due to technical difficulties (breakage in the centrifuge).

The amounts of DNA obtained after extraction of 7th nerve geniculate ganglion tissue varied between 6 gm and 58 gm total. Initial dot-blot assays used a total between 1.5 and 4.4 gm of DNA.

In both series of dot-blot controls were included as follows: a DNA extract from Vero cells which had been productively infected with herpes simplex virus strain SC16 (a type I). Two separate DNA extracts from tissue culture cells which were thymidine kinase deficient (TK) lines, designated 3T3 TK and LM TK.

All the geniculate ganglia tested by dot-blot were positive after 24 hrs for both Left and Right sides. See Autoradiograph 2.

It was decided to investigate patients 3-5 both R and L 7th nerve extracts by Southern analysis. The amounts of DNA used were limited to between 0.9 and 4.2 gm total. These extracts were digested with Bam H1 (Northumbria Biologicals Ltd) for 3 hrs prior to running overnight on a 0.8% agarose gel.

The controls included a DNA extract from Vero cells which had been infected with SC16 (HSV₁) and two negative controls 3T3 TK and LM TK as previously described. See Autoradiograph 3.

All clinical samples were positive after exposure for just 2½ hours. Two lines were produced in each lane, a stronger line approximating the Vero positive control and a weaker line of lower molecular wt. The single line produced on the Vero extract was lower than lines on the clinical specimens by some 3mm.

Autoradiograph 4 shows Southern analysis of trigeminal ganglionic extracts using the NBL enzyme Bam H1. Autoradiograph 5 shows Southern analysis of trigeminal ganglionic extracts using the Amersham International enzyme Bam H1. Fig. 6.5 (b) shows the corresponding DNA loading.

In order to check the NBL Bam H1 enzyme 5th nerve material was used for Southern analysis. Furthermore the TK probe was checked by electrophoresis and found to be the right order of size i.e. 3.6 kbp. See fig. 6.9.

HSV isolates from 4 clinical specimens were grown and total cell DNA extracted:

- 1) Vulval swab 87/2840 M.R.I. dept. G.U. Medicine
- 2) Penile swab 87/2842 M.R.I. dept. G.U. Medicine
- 3) Throat swab 87/2843 Patient with acute myeloid leukaemia
- 4) Penile swab 87/2953 M.R.I. dept. G.U. Medicine.

These were digested with NBL Bam H1 together with a standard HSV₁ (Syn17+) and TK controls. The samples were Southern blotted and probed with PA 29 and also PSG 22 and PSG 124. See Autoradiograph 6.

Results show that different biological strains of HSV migrate differently with HSV₂ strains migrating a little further than HSV₁.

Autoradiographs 7 and 8 show multiple lines with probes PSG 22 (13,000 kbp) and PSG 124 indicating their limited usefulness for the study - due to non-specific binding.

Subsequently success was obtained using the PA 29 probe with 5th nerve ganglion extracts from patients 1 and 2 using Southern analysis. Perfect alignment was shown in the radiograph (not included).

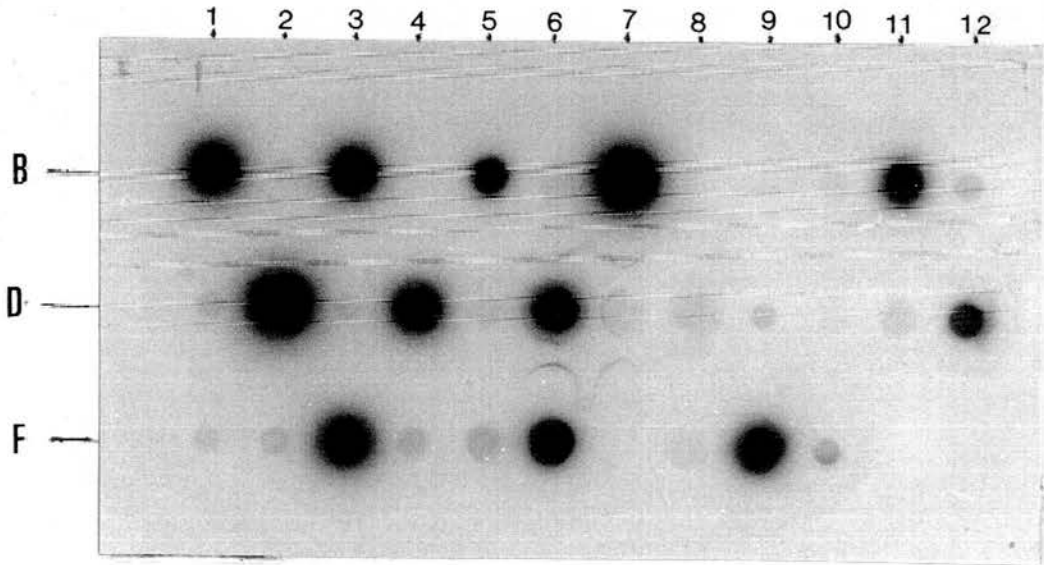
Vth nerve ganglionic extracts (PA29 probe)

		L - positive
patient 1	{	
		R - equivocal/negative
		L - positive
patient 2	{	
		R - positive

FIG. 6,1: AUTORADIOGRAPH 1

AUTORADIOGRAPH OF TRIGEMINAL GANGLIONIC EXTRACTS (CONTROLS) USING
DOT-BLOT PROCEDURE.

24hr exposure, probe 3.6kbp., Patients 3-20



Key:-

B 1-12: 3R, 3L, 4R, 4L, 5R, 5L, 6R, 6L, 7R, 7L, 8R, 8L

D 1-12: 9L, 10R, 10L, 11R, 11L, 12R, 12L, 13R, 13L, 14R, 14L, 15R

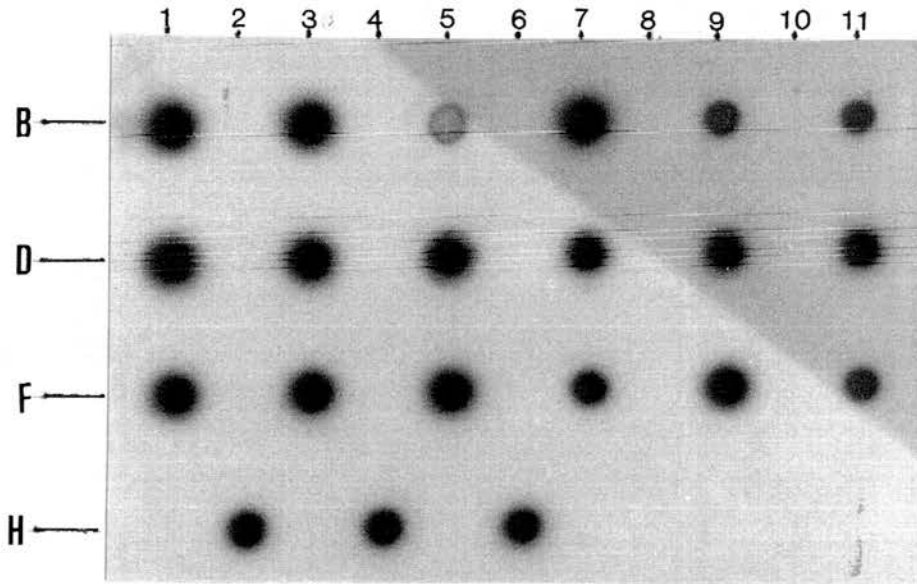
F 1-12: 15L, 16L, 17R, 17L, 18R, 18L, 19R, 20R, 20L, Vero

F10 Vero Positive Control

FIG. 6,2: AUTORADIOGRAPH 2

AUTORADIOGRAPH OF GENICULATE GANGLIONIC EXTRACTS USING DOT-BLOT
PROCEDURE

24 hr exposure, probe 3.6kbp, patients 3-12



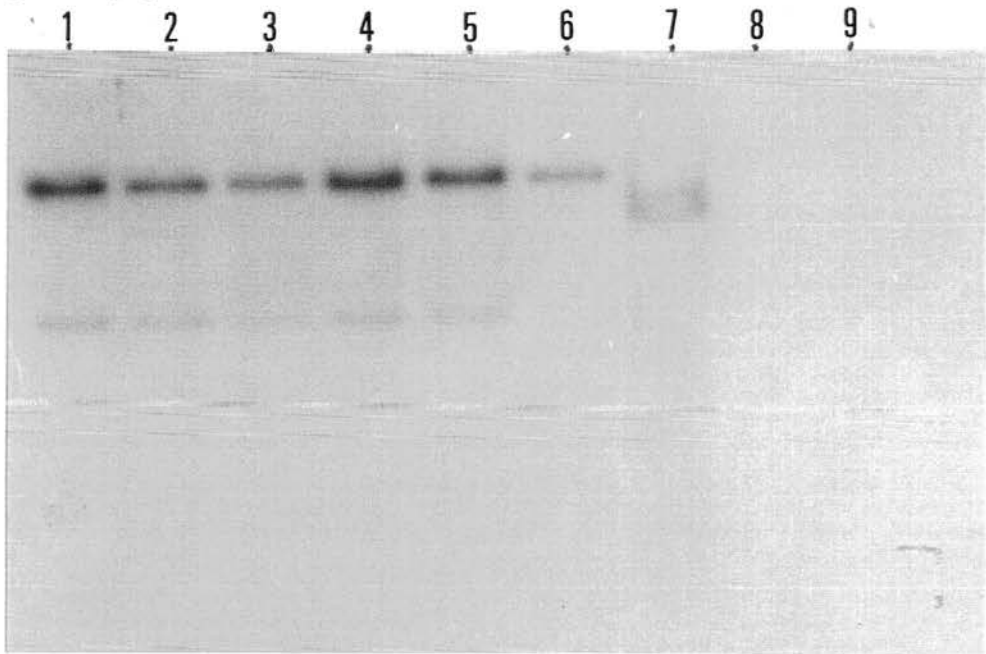
Key:-

B 1-11: (ODD NUMBER COLUMNS): 3L, 3R, 4L, 4R, 5L, 5R
 D 1-11: (ODD NUMBER COLUMNS): 6L, 6R, 7L, 7R, 8L, 8R
 F 1-11: (ODD NUMBER COLUMNS): 9L, 9R, 10L, 10R, 11L, 11R
 H2 - 12L, H4 - 12R, H6 Vero

H6 Vero Positive Control

FIG. 6,3(a): AUTORADIOGRAPH 3SOUTHERN ANALYSIS OF 6 GENICULATE GANGLIONIC EXTRACTS

17hr exposure, patients 3-5



Key:-

Key:-						CONTROLS			
Lane	1	2	3	4	5	6	7	8	9
	3L	3R	4L	4R	5L	5R	Vero POSITIVE	3T3 TK-	LM TK-

FIG. 6,3(b)

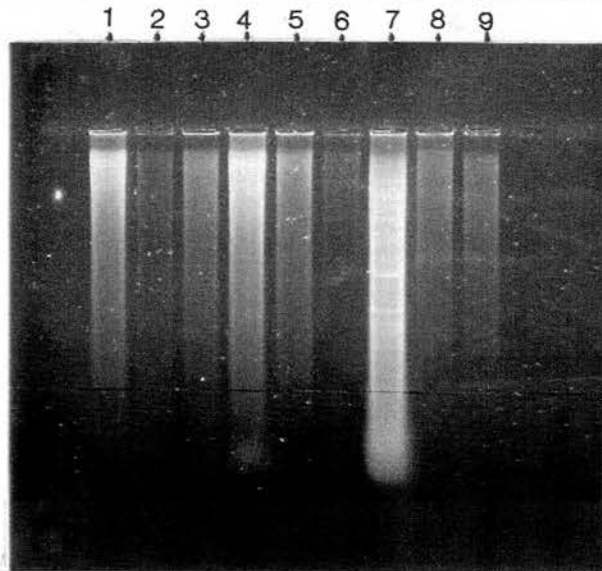
PHOTOGRAPH OF AGAROSE GEL SOAK, OF SAMPLES 1-9 (AS ABOVE)

FIG. 6,4: AUTORADIOGRAPH 4

SOUTHERN ANALYSIS OF TRIGEMINAL GANGLIONIC EXTRACTS DIGESTED BY
N.B.L. Bam H1

2½ hr exposure, patients 3-20

Samples from patients 3-20

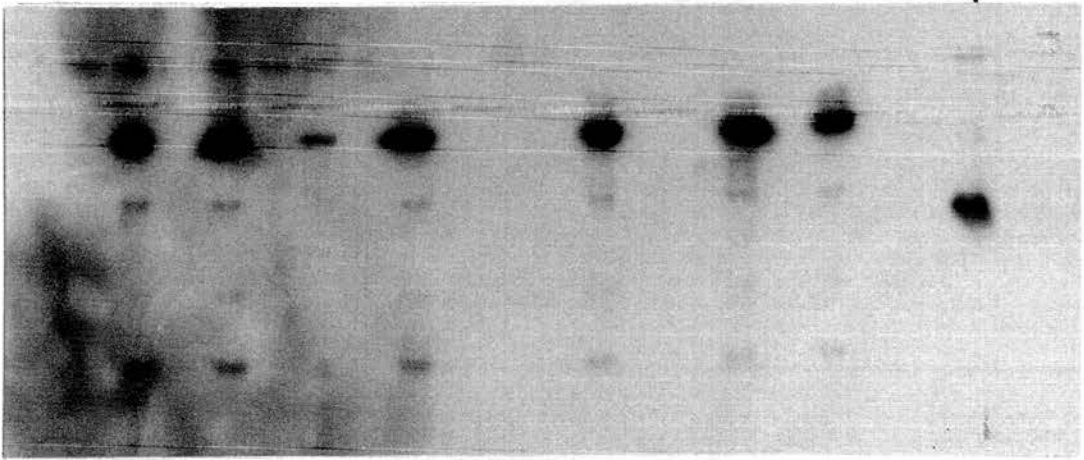
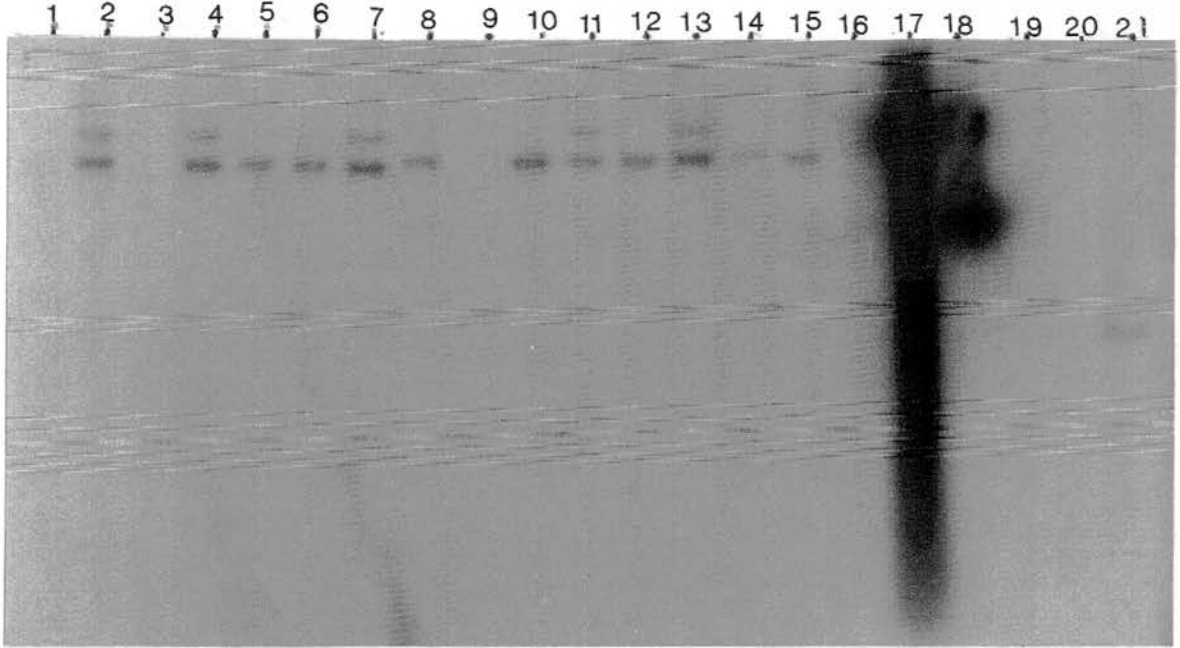


FIG. 6,5(a): AUTORADIOGRAPH 5

SOUTHERN ANALYSIS OF TRIGEMINAL GANGLIONIC EXTRACTS USING AMERSHAM
INTERNATIONAL Bam H1 Enzyme

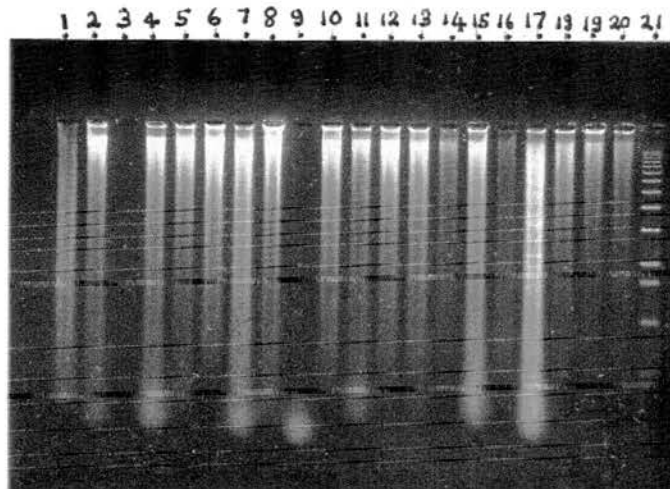
66 hr exposure, patients 3-20



Key:-

1	2	3	4	5	6	7	8	9	10
3L	3R	4L	4R	5L	5R	6R	7L	7R	8L
11	12	13	14	15	16	17			
8R	9L	10R	10L	11L	11R	Vero			
18-TK ⁻ and probe DNA gB,							19-3T3 TK ⁻ and TK,		
							20 3T3 TK ⁻ ,		
							21 Ladder		

FIG. 6,5(b): PHOTOGRAPH OF GEL



Key: as above

FIG. 6,6: AUTORADIOGRAPH 6

SOUTHERN ANALYSIS USING PROBE pA 29

2 hr exposure



Key:- 1 - HSV/Vero; 2 patient number 2840; 3 patient number 2842;
4 patient number 2843; 6 patient number 2953

FIG. 6,7: AUTORADIOGRAPH 7

SOUTHERN ANALYSIS USING PROBE pSG 22

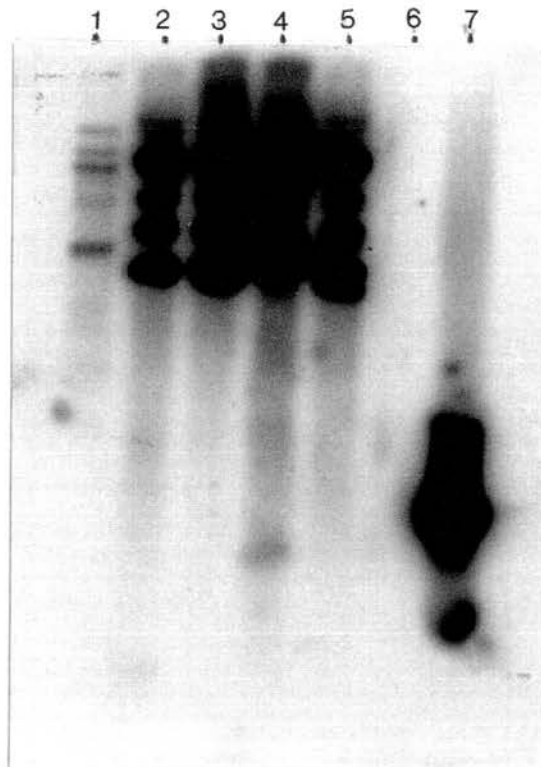
4 day exposure



Key:- as above

FIG. 6,8: AUTORADIOGRAPH 8SOUTHERN ANALYSIS USING PROBE pSG 124

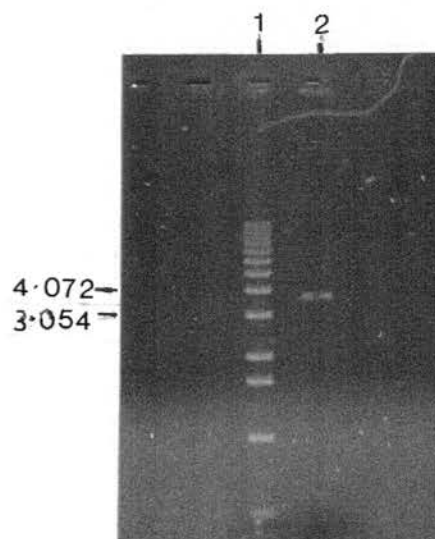
72 hr exposure



Key:- 1 - HSV/Vero; 2 patient number 2840; 3 patient number 2842;
4 patient number 2843; 5 patient number 2953; 7,1kb ladder

FIG. 6,9:

PHOTOGRAPH OF GEL ANALYSIS FOR 3.6kbp PROBE FROM BETHESDA RESEARCH
LABORATORIES



Key:- 1 - kb ladder, 2 - probe between 4.072 and 3.054 kbp

CHAPTER 7

Discussion of studies attempting to isolate or detect HSV
from human post mortem geniculate and trigeminal ganglia

7.1 Literature Review of Isolation of HSV from 1° Afferent Ganglia

That HSV resides in latent form in sensory ganglia was suggested by Carton in 1952 who noted the appearance of HSV lesions around the mouth immediately post-operatively following root section for trigeminal neuralgia.

Further rationale for studying the trigeminal ganglia is the fact that recurrent HSV lesions affect predominantly the oral and genital mucosae and hence the trigeminal and sacral ganglia are the most likely sites for viral persistence (or latency).

The first successful isolation of HSV from human trigeminal ganglia was made by Bastion, Rabson, Yee and Tralka in 1972 using an explant technique, with 2 out of 23 cadavers yielding reactivated virus from ganglion neurones.

Baringer and Swoveland in 1973 using a similar methodology isolated HSV in 6 out of 7 cadavers, 8 out of 13 ganglia. The ganglia were obtained at post-mortem less than 12 hours after death and maintained in culture for 10-45 days. The ganglia were removed in sterile fashion as soon after death as possible to ensure increased viability of ganglion cells. The ganglia were minced finely, and washed twice in Hank's balanced salt solution. The specimens were then centrifuged and resuspended in Leibowitz medium L-15 with 20% foetal calf serum added. The suspensions were inoculated into 25ml plastic Falcon flasks, and maintained at 36.5°C with medium changes twice weekly and observed for cytopathic effect; cytopathic effect being a specific response of cells to HSV.

The supernatant was frozen at -70°C or direct assay was made for virus by adding 1ml of ganglia medium onto monolayer cultures of primary rabbit kidney. Immunofluorescent and neutralizing antibodies (anti HSV hamster 1gG) were used to type the virus. The presence of virus was also confirmed by electron microscopy studies. Positive results were obtained 10 to 45 days after explanting in 8 out of 13 ganglia studied.

Rodda in 1973 isolated HSV from the trigeminal ganglion of 1 adult cadaver but not in 5 children. The ganglion yielding the positive culture was removed at 9 hours after death. With the appearance of cytopathic effect passage was made to Green Monkey kidney cells (Vero line), or human embryonic fibroblasts. The author stressed the importance of maintaining cultures for 3 months with cytopathic effect usually occurring at around 1 month.

Plummer (1973) was also able to isolate HSV from trigeminal ganglia of man, monkeys and cats by co-cultivation, with primary rabbit kidney; with isolates occurring between days 8-43 (4 out of 10 human ganglia yielded HSV).

Baringer (1974) isolated HSV from 4 out of 26 cadavers, identifying HSV type II from the third and fourth sacral ganglia. There were no successful isolates from 21 thoracic ganglia. In this study trypsinised human embryonic lung cells (flow 2000), L₁₅ medium, and 10% foetal calf serum were added to minced ganglion extracts.

Warren in 1977 isolated HSV from 18 out of 39 trigeminal ganglia obtained within 12 hours of death, including a patient who had died with multiple sclerosis. The following year Warren made a successful isolation of HSV from the superior cervical ganglia and the jugular portion of the vagus ganglion from one cadaver.

Only one study so far has looked at isolation from the geniculate ganglion of humans. Degré in 1978 isolated HSV in only 3 of 20 trigeminal ganglia and in none of the 20 geniculate ganglia studied. The method used was that of Baringer, 1974.

HSV was isolated from human trigeminal nerve roots by Warren in 1982 (6 positive isolates from 18 patients) suggesting that latent HSV is not just confined to autonomic and sensory ganglia of humans. The coeliac ganglion was also noted as a site by Rand (1984) who successfully isolated HSV in a patient dying after renal transplantation.

Overall the isolation rate for HSV varies between 40-80% of the trigeminal ganglia studied (Baringer 75, Warren 77, Brown cited by Degré

78, Lewis 82). The highest frequency of isolates were found in the 'freshest' specimens with the worst rate 15% quoted by Degré, in specimens more than half of which were obtained over 24 hours from the time of death. Necrolysis it would thus appear adversely affects the isolation rate.

On reviewing the literature for human cadaver material, HSV has been successfully isolated using explant and co-cultivation techniques from trigeminal ganglia, but not from the geniculate ganglia - although only one study attempted to do so. The paucity of information about geniculate ganglia almost certainly relates to the considerable difficulties in obtaining specimens. This lack of information can be supplemented by considering animal studies. The work of Thomander 1988 has already been mentioned, and of further interest is the work of Hill and Blythe 1981 who failed to isolate HSV from facial ganglia in outbred mice using co-cultivation techniques. They obtained positive cultures in the 31 mice examined in 8 trigeminal, 8 vagal and 20 pooled cervical ganglia.

7.2 Background to the Hybridization Study

The two main methods used in this study, cocultivation and blot hybridization, are comparatively assessed by Gordon 1984. There have been no attempts to identify HSV genome by DNA/DNA hybridization techniques from the geniculate ganglia of human cadavers and only one study to date, that of Efsthethiou S. et al (1986), has used this technique for examining the sequences of trigeminal ganglia DNA extracts obtained at post mortem.

Fraser et al (1981) and Saldanha (1986) have detected HSV virus DNA in human brain extracts but most of the experimental evidence for this technique still comes from animal work. Wigdahl (1984) detected linear HSV DNA in in-vitro mice with established latent infection, inoculated by the corneal route, finding sequences in trigeminal ganglia and brainstems. Puga (1984) used a similar model and detected fragments of 'uncharacteristic' size, suggesting that rearrangement of viral sequences had occurred within the host cell, or that integration with cellular DNA had been at more than one, but nonetheless at a restricted number of sites.

More recently attention has focused on detection and mapping of HSV RNA's in animal models (Rock 1987, Rosen-Wolff 1989).

In summary the literature on DNA/DNA hybridization techniques for HSV genome in human neural tissue is sparse, although recombination DNA technology has been considerably developed over the past 10-15 years (Glover, D. 1984). It remains, however, a costly technique and specialised knowledge of both virologist and clinician are needed in obtaining and processing human specimens in a satisfactory manner. Efsthathiou's work has shown that HSV genome can be reliably demonstrated in cadaveric trigeminal ganglia - in 11 out of 20 specimens or 55% - which can be used as a 'standard' by which the control result from this study can be assessed.

7.3 Cocultivation Study - Discussion and Summary of Findings

To isolate HSV from the geniculate ganglia obtained at post mortem several techniques may be used. Historically co-cultivation was the first successful method for isolating HSV from primary afferent sensory ganglia. The study here outlined was conducted by the author as an initial attempt to isolate the virus.

The techniques used became problematical with microbial overgrowth in specimens occurring regularly precluding reliable observation for cytopathic effect, and preventing any meaningful conclusions being drawn from the study. Co-cultivation was also performed by an experienced technician who ran into similar problems as the author with evidence of microbial contamination affecting most specimens after several days.

A considerable number of specimens were processed in this way - 72 in all, 36 trigeminal and 36 geniculate ganglia. Recordings were made on a cocultivation study data sheet (Appendix 4d).

In an attempt to overcome the problem the following steps were taken:

- 1) Specimens taken at post-mortems performed shortly after death wherever possible;
- 2) Aseptic techniques used despite their limitations in the post-mortem room; fastidious cleaning of instruments and work surfaces in temporal bone room, and use of non-touch techniques; fastidious cleaning of surfaces in virology laboratory side-room with closure of air-vent, and use of non-touch techniques.

Despite these steps contamination continued to occur. It was felt there were two main reasons for this.

Firstly the condition of the specimens was not generally speaking good and initially in the study, many older i.e. over 36 hrs. after death, specimens were used. On removal many specimens showed macroscopic evidence of necrolysis.

There was good rapport with the pathologists at M.R.I. but despite considerable efforts no specimens could be obtained at 12 hrs or less after death. This was later achieved during the DNA hybridization study because of a serendipitous move towards earlier post-mortems at the time that the second study was being carried out.

Secondly, in discussion with Prof. Longson it was acknowledged that the University building air ventilation system had also caused problems for other research projects with a high level of airborne fungal contamination occurring.

The contamination continued to occur despite switching specimens to the regional virus laboratory and so it was surmised that the main reason for failure was the poor condition of the specimens obtained, and the fact that it proved impossible to prevent early microbial contamination in the post-mortem room and temporal bone room. The medium 'fungizone' was used for transport throughout at a concentration of 5 gm/ml. Higher concentrations could not be used as they would affect the cell growth of the culture.

Had the alternative of DNA probing not become available to the author during the study period he would have attempted to identify the source of microbial contamination more precisely. If necessary and by further negotiations, a switch to a different hospital conducting earlier post mortems might have been relevant.

However during the study period Dr. G. Corbett was able to provide the facility of processing the specimens by the method of DNA/DNA hybridization for HSV genome. Subsequently 80 specimens were provided for investigation by this method, thereby diminishing the magnitude and the type of problem from microbial contamination.

7.4 Discussion of Results of DNA/DNA Hybridization Study with Critique of Methodology

In view of the widely accepted idea that the dorsal ganglion of the 5th nerve harbours HSV it was reasoned that prior to probing 7th nerve samples we should show our ability to detect HSV sequence in 5th nerve ganglia.

The reason for employing dot-blot analysis before Southern analysis was because to detect single copy genes by the latter technique DNA has to spread down agarose gel, and 10µgm of DNA is needed as a minimum whereas for a single spot of DNA concentrate, less is required.

Autoradiograph 1 shows that the control material (trigeminal ganglionic extracts) were strongly positive in 12 out of 36 ganglia (33%); 4 out of 36 (11.1%) were negative; the remaining 20 (56%) ganglia were weakly positive. The Vero positive control containing HSV DNA in a total cell DNA extract appeared of similar density to the weak positive results. Thus 32 of 36 ganglia or 89% of trigeminal ganglia were positive.

A possible reason for the increased density dot-blot or strong positives might be that HSV reactivation occurs around the time of death as part of the terminal illness, or alternatively it might be argued that the strong positives are true positives and that the weak positives are difficult to interpret because of non-specific probe binding to cellular DNA. Dr. Littler who provided the probe had no evidence that the probe was likely to bind to cellular DNA. Furthermore the TK-control showed no evidence of binding at any stage suggesting there was no non-specific uptake. Efsthathiou's finding of 11 out of 20 positives (55%) is a broadly comparable finding given the small numbers involved in both studies and using "predictions" from co-cultivation studies. It was felt however that on balance there was probably a 'faint background' representing non-specific binding.

Autoradiograph 2 shows that all the geniculate ganglia were positive on dot-blot analysis and of varying autoradiographic densities. 19 out of 20 were strongly positive and one was more weakly positive. The finding that all geniculate ganglia were positive was difficult to accept as 'specific', therefore the membrane was rewashed at very high stringency 0.1 x 5.5c, 68°C for 1 hour, and using two separate washes. After placing to film after only 3 hours exposure it was shown that all dot-blot were still giving a positive signal.

It is argued that the stringency of the methods employed tends to confirm the specificity of the technique, and that binding of the probe to the extracted DNA was very strong indeed. These results suggest that HSV genome resides in geniculate ganglia of the 'general' population and that it does so at a higher frequency than in trigeminal ganglia.

To further support the findings of the dot-blot method geniculate ganglionic extracts were examined by Southern analysis as were controls (trigeminal extracts).

Autoradiograph 3 shows a strong positive response of the geniculate ganglia compared to the Vero positive control and with appropriate negative results from the 2 controls 3T3TK and LMTK. The increased electrophoretic mobility of the Vero positive control by some 3mm is problematical to the study and difficult to interpret, suggesting a lighter combined M.W. for the control. One possible explanation for this could be the much heavier DNA loading of the Vero extract exerting a "pushing" effect during electrophoresis and therefore moving the TK line further with respect to the clinical samples. See figure 6, 3(b).

A further consideration is that the specificity of the probe is all important. If it is not 100% specific it can lead to 'odd results', if plasmid remains bound to it.

The possibilities that different strains of HSV migrate at different rates is a further explanation, and this is discussed later (vide intra). A fourth possible explanation is that like the measles virus HSV can become altered with time in its state of persistence in neurones, thereby exhibiting different characteristics when analysed by hybridization, and this is discussed in Efsthathiou's paper (1986). Puga (1984) noted variation in size of the terminal fragment (Eco R₁) but not the Bam H₁ fragments.

A second faint line was present in all the clinical samples. The reasons for this are not clear. However Efsthathiou, obtaining a similar 'double line', suggested homologous sequences in the cellular material and obtained similar results with hepatic as well as neural tissue. This protein is absent in the Vero cell controls. If the cadaver material was contaminated by bacterial growth a further explanation may be given. That is, the DNA extracted would be a mixture of HSV

DNA, cellular DNA, and bacterial DNA. As the probe used is amplified in *E. coli* plasmids it is possible that sequences of probe DNA have *E. coli* DNA contamination, and this is homologous to the sequences in the contaminated extracted DNA. Therefore the second faint line may be due to contaminating bacteria and not HSV. Although this is a possible explanation, on balance it is felt to be very unlikely because the same contaminant would be consistently required in every specimen, taken over a period of several months.

Autoradiograph 4 shows unusual results and it was concluded that NBL Bam HI was not a very good enzyme preparation, and was cutting DNA badly. None of the positively labelled DNA lines match up to the control.

Autoradiograph 5 shows Southern analysis of 5th nerve material using the Amersham International Bam HI enzyme, using tissue samples 7 to 11, left and right specimens. Again, several lines were produced in the radiographs. It was decided therefore to use a different probe DNA.

A new clone (bacterial and probe DNA within plasmid) designated PA29 was obtained as a kind gift from Dr. S. Efsthathiou of Cambridge. This carries a small 800bp fragment of the Bam HIQ fragment of HSV DNA, and contains sequences specific to part of the TK gene of HSV, and amplified and purified for use.

In an attempt to determine possible variability between strains, four laboratory HSV isolates were grown up and the total cell DNA extracted. Autoradiograph 6 shows that different strains of HSV migrate differently with HSV₂ strains migrating a little further than HSV₁. However, the standard HSV₁ had previously migrated ahead of the ganglionic extract. Such differences in electrophoretic mobility between strains would therefore be a possible but unlikely explanation for the 3mm misalignment reported earlier. - considering the general rule that HSV₁ has a proclivity above the umbilicus and HSV₂ below it!

Two further probes PSG22 and PSG124 were tested but provided limited usefulness to the study because of non-specific binding.

The PA29 probe proved to be the most promising with respect to good alignment on Southern analysis of the 5th nerve ganglionic extracts.

Unfortunately due to funding problems further clarification of the Southern analysis results will depend on these becoming available.

The next rational step would be to further process the available specimens of geniculate and trigeminal ganglia using the more highly specific PA29 probe to determine the repeatability of the findings.

The results of the dot-blot tests and the finding that the positive control rate was 32 out of 36 for this study and 11 out of 20 for Efsthathiou's study is broadly comparable, and furthermore close to that predicted by co-cultivation studies - 60%, - and seroconversion studies suggesting at least 90%.

The surprising finding that all the geniculate ganglia tested out of a sample of 20 on dot-blot analysis were positive, can from the limited evidence here presented be most logically explained by the fact that, in this particular small sample of the population, all the patients were harbouring HSV DNA in their geniculate ganglia. If non-specific binding to neural tissue were always occurring then all the control material should also have been positive.

Serology would have been a useful adjunct in demonstrating false positives obtained by the hybridization study even though 90% of the population over 30 years of age are likely to have demonstrable antibodies to HSV. In Efsthathiou's paper 4 out of 20 had $<1/10$ titre to HSV (by reverse passive haemagglutination). A possible explanation may be that HSV may gain entry to the nervous system more readily and with little if any immune response, through a mucosal surface as opposed to a keratinized surface. It is also argued that uptake by taste-bud neurones in the anterior $\frac{2}{3}$ of the tongue may occur, allowing invasion of the CNS via the chorda tympani, geniculate ganglion route. Thus the virus may creep 'silently' to residence within the geniculate ganglia without much or indeed any inflammatory reaction occurring. This would either require that HSV has a predilection for the geniculate ganglion neurones to the extent of perhaps limiting its spread within the CNS. Or alternatively immune factors may become important in curtailing spread within the CNS. Clarification of the surprising findings of this study and their implications must rest with further hybridization studies, using reliable specific probes on ganglionic material.

PART II OF RESEARCH

**Epidemiological Studies of Bell's Palsy
in British General Practice**

CHAPTER 8

Epidemiological Studies of Bell's Palsy - Materials and Methods

8.1 Introduction

The studies comprise a descriptive and a case-control study. Bell's palsy cases were selected by means of a prospective case-finding method with new cases notified over a one year study period.

For the purposes of the studies a case of Bell's palsy might be defined as:-

"a motor weakness to the face perceived or brought to the attention of the patient, which resulted in a consultation with a participating GP who had to "diagnose" or more correctly recognise the condition and notify the department. These cases were then checked by the author using stringent clinical criteria, and also information from 6 month follow-up to exclude latent specific pathology; as a means of ensuring that the sample of cases was acceptably specific".

Ethical approval

Ethical approval for this study was sought and obtained from the Manchester Royal Infirmary, Regional Ethical Committee, for which details of the study were outlined and the questionnaires used submitted. Permission was requested to study the general practitioners' patients and take blood samples. Steps were taken to assure all patients and controls of full confidentiality.

8.2 The Descriptive Study

8.2.1 Materials used:

Letters in the study

- 1) Letters to individual FPC's
- 2) 1st letter to GP's (requesting compliance) background to study (Appendix 2a), completion sheets (Appendix 2b).
- 3) 2nd letter to GP's (reminder) (Appendix 2c), completion sheets (Appendix 2d)
- 4) Follow up letter to patients (at 6 months) (Appendix 2e)

Pre-paid reply envelopes for all of the above.

Letters to individual patients - arrangements for visiting.

Transport (car) and A-Z of Greater Manchester area.

Bell's palsy case questionnaire (Appendix 1a)

Self administered - Schedule Recent Event, checklist (Appendix 1c)

Map of Greater Manchester for marking cases.

Examination materials

Briefcase containing:-

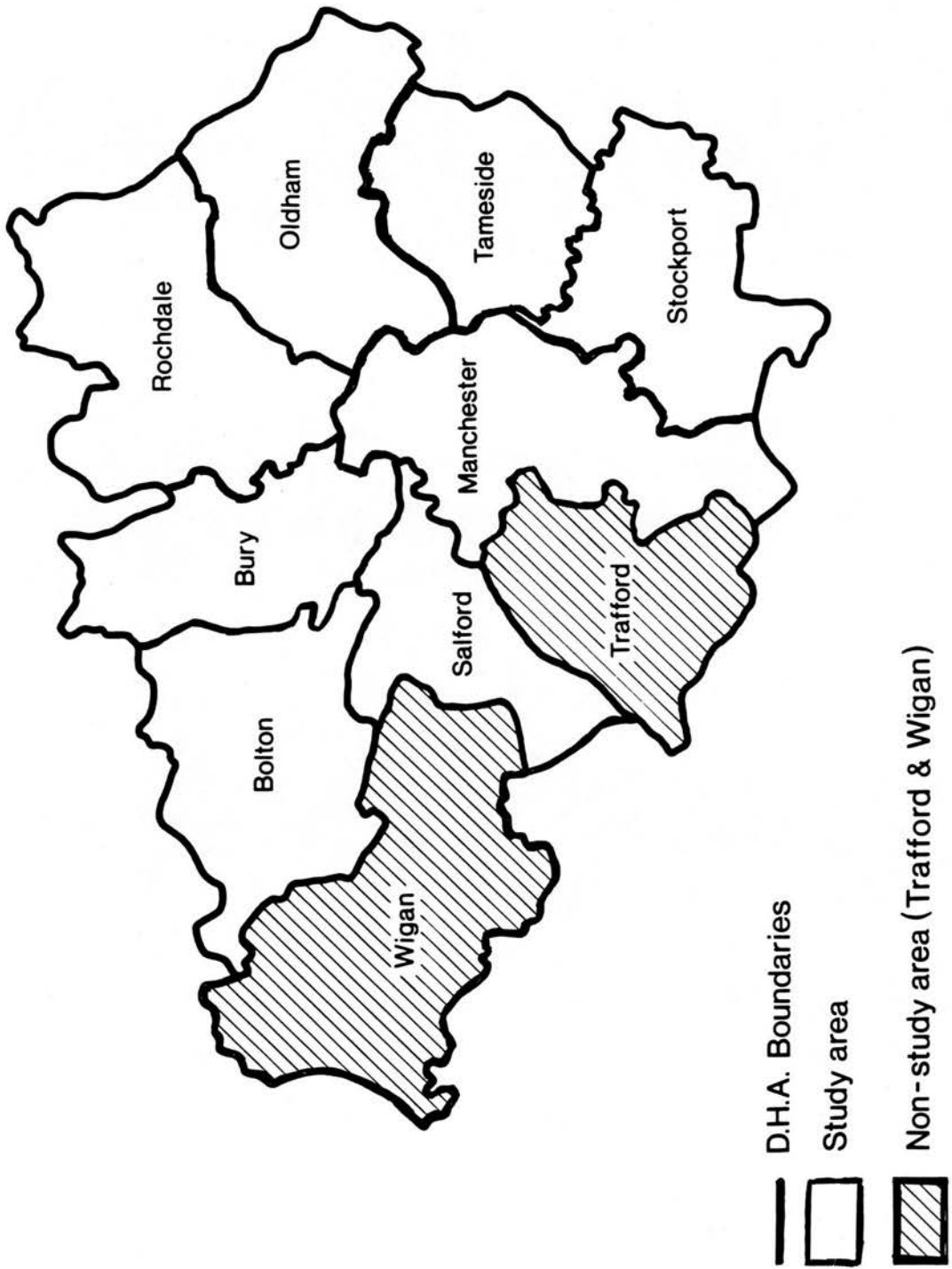
- 1) Wooden spatulas
- 2) Keeler auroscope/light source
- 3) Cottonwool and hatpin
- 4) Tourniquet
- 5) Alcohol wipes
- 6) Green needles
- 7) 10ml syringes
- 8) 10ml serum bottles
- 9) Virology cards
- 10) Labstix
- 11) Prepaid parcels containing 10ml bottle/virology card for a 2nd sample.
- 12) Canon camera and flash unit.

8.2.2 The denominator - the population under study, and statistical considerations

Statistical advice was sought early for the study from Dr. Lucas of Manchester University Department of Medical Statistics. The estimated incidence of Bell's palsy from European studies was taken as approximately 20 per 100,000 per year. The aim of the study was to recruit 100 cases of Bell's palsy over 1 year, which entailed finding a minimum study population of 500,000. This number would allow a reasonable descriptive study to be performed. If a similar number of controls were found then the study would have the power to test aetiological variables such as preceding depression and URTI, and examine HSV disease itself (cold sore history) for any strong associations. Given the resources of the study a larger and more powerful study of this relatively rare condition was not felt to be feasible.

10 FPC AREAS OF GREATER MANCHESTER

Fig. 8.1



General practitioners were invited to support the study by a letter distributed by the FPC's (Appendix 2a). The 10 FPC's of Greater Manchester were contacted by letter for cooperation with the study (fig. 8.1).

8.2.3 Characteristics of the Greater Manchester population

Between 1971 and 1981 the OPCS reports a decrease of 4.9% of the population compared with an increase of 0.5% for England and Wales. There were 20.17 persons per hectare in Greater Manchester compared with a provisional estimate of 3.24 for England and Wales. Manchester 38.61 was the most densely populated part of Greater Manchester despite a decrease of 17.5% of the population in 10 years, whereas Rochdale at 12.98 was the least densely populated, but with an increase of 2.1% of the population. The proportion of under 16's varied from 24.5% in Rochdale to 21.6% in Manchester. The proportion of persons of pensionable age was highest in Manchester 18.9% and lowest in Rochdale 15.7%.

Overall 5.8% of the usually resident population were born outside the United Kingdom, and the Manchester population contained the highest number of immigrants per region at 11.2%. The unemployment level for Greater Manchester was 12.6%. The lowest incidence was in Stockport 8.5% and highest in Manchester at 18.1%. Households where no car was available also varied from 34.6% in Stockport to 60.4% in Manchester. Overcrowding as defined as more than one person per room was highest in Manchester 5.7%, with a mean of 4.0% for the county.

8.2.4 Letters to the General Practitioners and notification of cases

A standard letter was sent to individual practitioners via the appropriate FPC (see tables 4 & 6). Part-time practitioners were not included in the study. The letter contained an invitation to help with the study and an explanatory letter to encourage compliance and interest.

Table 4: Letter distribution to individual FPC's

Manchester Central	280	Bury	86
Salford	170	Bolton	130
Tameside	100	Oldham	115
Stockport	140	—	
Rochdale	100	Total	1,121

Agreement to notify new cases was signalled by return of a completed sheet indicating agreement (Appendix 2b) to the Department of General Practice of Manchester University at Walmer St., Rusholme, Manchester. The practitioner needed to inform the department by telephone or letter of any new cases, and provide details of patient address, phone number and date of onset.

Individual practitioners had to:-

- 1) Actively remember study is in progress
- 2) Be capable to diagnosing Bell's palsy
- 3) Secure agreement with patient to be studied
- 4) Notify the department.

Notification of the department by this method was necessary because Bell's palsy is not a notifiable disease in the usual meaning of the word. The patient would then be contacted by phone usually, or letter occasionally, and a visit requested by the researcher (the author). This usually took place within 3 weeks of the onset of the paralysis.

A further letter was sent on 2nd March 1986, 8 months into the study to serve as a reminder (Appendix 2c). However this letter also asked for a reply giving further details. The hypothesis was formulated that if the General Practitioner did not reply to this letter it would be unlikely that he was reporting any new cases of Bell's palsy he had seen to the department. The details of the reply also allowed more accurate information to be adduced about the study population. This included list size and whether reported cases had been on the GP's list or a partner's list.

The second letter also asked the GP if he had reported all new cases and if he hadn't if he had forgotten the details, or could remember them but the patient did not wish to be referred.

A list of participating GP's is given in Appendix 3b and those who replied at 8 months are denoted by an asterisk. '1 case' indicates referral of a case into the study. Of the participating GP's some were in single and some in group practice, only a small proportion of the replies indicated that they would report cases seen by their partners. Although GP's see patients primarily on their own lists, a personal list system is certainly not ubiquitous, and particularly in "urgent" situations a personal list system is put under more strain. To obtain more accurate information therefore 2 steps were taken.

Table 5Starting and finishing dates for individual FPC areas

<u>FPC</u>	<u>Start date</u>	<u>Completion date</u> (12 months)
Tameside	16/6/85	16/6/86
Bolton	28/6/85	28/6/86
Bury	25/6/85	25/6/86
Rochdale	15/6/85	15/6/86
Stockport	25/6/85	25/6/86
Salford	28/7/85	28/7/86
Oldham	12/7/85	12/7/86
Manchester	30/7/85	30/7/86

Reporting encouraged for all doctors until 31/7/86 - no cases needed to be excluded because of reporting after the completion date.

- 1) Patients who were referred were asked did their own doctor refer them? This was then checked against the list of original replies.
- 2) At 8 months a second letter specifically asked the participating doctors if they had referred a case had the patient been on their own or their partner's list?

8.2.5 Geographical factors

All reported cases were located within a 16 mile radius of Manchester Town Hall or 18 mile radius of Rusholme Health Centre (Univ. Dept.). The twin cities of Manchester and Salford lie at the North Easterly edge of the Cheshire plain. The lower reaches of the Pennines encroach on the North Eastern parts of the conurbation. Most patients were referred from either urban or industrial town practices with very few from more rural practices.

8.2.6 Time scale of the study

It was determined that the study should be of 1 year duration. The main reasons being:-

- 1) For a large General Practice based study a short study period increases the compliance and improves the accuracy of the reporting.
- 2) The aetiological factors being studied in this acute condition might be expected to act in short periods from hours to months before the onset.
- 3) Speed of acquisition of data.

The disadvantages to this time-scale include:-

- 1) The incidence of the disease cannot be related to broad trends e.g. in HSV epidemiology.
- 2) Fewer cases.
- 3) Evaluation of seasonal trends more difficult.

Different FPC's sent out the letters to GP's at different times. The time the first GP from an FPC area replied being taken as the commencement date (the FPC's sent out all the mail usually within 48 hours). This varied from mid-June 1985 (Tameside) to the last week in July 1985 (Manchester) (see Table 5). The closing date was given as August 1st 1986. This included a prolongation of the 1 year period by several weeks for most FPC areas in which patient delay in presentation could be absorbed.

8.2.7. Responses of FPC areas and General Practitioners

10 FPC areas of Greater Manchester were contacted. Of these 8 responded positively from the outset; Manchester Central, Salford, Tameside, Stockport, Rochdale, Bury, Bolton and Oldham (appendix 3a). Trafford FPC did not respond to the original letter or subsequent communications, Wigan refused to help with the study, but revoked this decision 4 months after the study had commenced - however this FPC was not then included.

252 GP's agreed to support the study, with an average list size of 2,200 (FPC figures) giving an estimated study population of 550,000 at the start of the study. Information from the 1981 OPCS census of Greater Manchester gives a figure of 2,575,407 persons usually resident. Thus approximately 20% of the population of Greater Manchester appeared to be available for the purposes of the study. More detailed information was available from the 144 GP's who positively responded to the second letter.

Table 6 - (see results p. 100), shows responses for individual FPC areas by GP's to an initial letter and also one sent 8 months into the study.

8.2.8. Exclusions from the study

Apart from those due to time of onset of the palsy. The exclusions were as follows:-

- 1) 2 patients referred within 2-3 weeks of each other by separate Salford GP's of cases of Ramsay Hunt syndrome where an auricular zoster rash was in evidence as well as a facial palsy.
- 2) One patient excluded herself from the study and expressed annoyance when visited that her general practitioner had referred her.
- 3) 2 suspected cases could not be contacted. One patient in Rochdale did not respond to two letters sent to his home address. The other had an incomplete address forwarded and the practitioner proved difficult to contact and was finally unhelpful.

8.2.9 Outcome assessments

The following outcomes were studied:-

- 1) Severity and duration of paralysis
- 2) Associated clinical features

- 3) Treatment type and commencement
- 4) Hospital referral
- 5) Recovery of paralysis - gradation and assessment
- 6) Recurrence

8.2.10 Follow-up arrangements

In the study several different types of follow-up were required. Firstly some patients were selected for paired anti-sera for the antibody study and this necessitated the patient's own GP seeing the patient 2 weeks later. The patient was given a prepaid parcel with 10ml serum bottle, virology card and explanatory/request letter for the GP (or contact was directly by phone in place of this letter).

After a minimum of 6 months had elapsed patients were sent a further letter in the form of a short questionnaire asking details of recovery (Appendix 2e). Patients were also contacted by telephone where the replies appeared unclear or no reply to the letter had been made. The duration of the paralysis was confirmed, where this information was still needed, as were details of hospital treatment and follow up. Only one patient was lost to follow up.

8.2.11 Contact enquiry and evidence of clustering

All patients were asked about contact with other people who may have had Bell's palsy in the past year including family members, associates at their place of work, and socially. Pursuing HSV as a possible aetiological agent the following selective questions were asked as part of a limited enquiry:

- 1) had the patient recently kissed someone with cold sores?
- 2) suffered from genital herpes infection?
- 3) had cold sores recently?
- 4) had symptoms of Acute Gingivo Stomatitis (AGVS) recently?

Patients were questioned about possible HSV contacts and in particular children as a source of infection, perhaps bringing a different strain of virus into the household. An enquiry was also made if appropriate as to which schools the children attended.

8.3 The Case-Control Study

Control data was needed for the aetiological study which could then be most appropriately analysed by match-pair analysis to examine for differences in associations between the groups. The materials used in this study include the control population, and the control and SRE questionnaires (Appendices 1b, 1c).

8.3.1 Selection of controls

This represents one of the most difficult parts of the methods as the aim was to find a similar group to cases except for exposure.

An equal number of controls as cases (80 of each) were found. It was decided that controls should not be patients attending surgery as this selective process would be prejudicial to the results. However patients listed with participating general practitioners i.e. on their lists should be approached at home for completion of the questionnaire in a similar fashion to those with Bell's palsy.

Controls were matched for age (by decade) and sex to eliminate effects of these confounding variables. It was also decided to match broadly on social group (groups I and II; III and IV; V and VI).

To some extent this might represent over-matching of controls for certain aspects of the study as HSV primary infection is related to social group with lower social groups experiencing primary infection at an earlier age. However neural reactivation of HSV which occurs after a state of viral persistence e.g. latent period does not appear to be directly related to social group. The value of matching by social group would make differences found e.g. in stress, drinking behaviour, U.R.T.I. etc. more significant.

Control data was not used for menstruation or pregnancy and control serum samples were not taken.

For logistical reasons, as only 1 observer (the author) was available for the study, a small sample of the practices compliant with the study were used. This sample was not taken randomly. The listed patients of

3 doctors at the university practice were used as a source, together with the listed patients of 2 single handed practices where the author worked as a locum in an area east of Manchester centre 6 miles and 13 miles respectively. All 5 doctors had agreed to notify cases of Bell's palsy and the combined list size was 11,402. As the university inner city practice might be described with respect to listed patients as more 'unusual' e.g. with very high numbers of young people and students and low social group, attempts to offset this were made by matching for age, sex and social group and also in the proportion of controls collected from this practice 20 (list size 7,340). The number from the Ashton practice was 42 (list size 2,742) and from Hadfield 18 (list size 1,320).

The case notes were taken haphazardly rather than in truly random fashion from the shelves and patient details of age, sex, and occupation sought (and checked-in the university practice only - if the GP had agreed to participate). These were checked against a 'Tally card' of Bell's palsy patients and crossed off when appropriately matched. The patients were usually phoned for an appointment but a few had letters. There was also a delay between recruiting cases and controls. For practical reasons controls were recruited into the study from October to August with a "seasonal" delay of about 2-3 months for match-pairs (a relative surplus of cases did however make it easier to find controls).

8.4 The Study Questionnaires

2 questionnaires were used in the epidemiological study, one for cases and one for controls. In addition supplementary information was obtained from a schedule of recent events check list (See appendices 1a, 1b, 1c). The patients were visited in their homes to encourage compliance and minimise loss of information. In addition assessment of the patient in their home gave more social, community and geographical information.

8.4.1 Piloting the questionnaires

It was first necessary to pilot the questionnaires to iron-out problems and reduce superfluous information. No cases of acute Bell's palsy were seen by the author following formulation of the draft questionnaire, and its introduction at the beginning of the study - mainly due to the relatively rare nature of Bell's palsy. It was decided to critically assess therefore the first 3 or 4 questionnaires completed. However it

was possible to pilot the control questionnaire, a shortened and slightly differently worded version of the case questionnaire. In addition comments from colleagues were invited and changes made to the drafts. The comments from colleagues were most useful in revising the questionnaire and questions like 'is there a past history of alcoholism' were changed to 'drink problem' - a more acceptable question to patients and placed lower in the order of questions because of its negative valuation. However the most substantial changes came from piloting on 10 patients attending surgery who were willing to answer questions used in the control questionnaires. The main change was in rewriting and reformulation of questions in a way which involved less medical jargon, and could be more readily understood by patients. In addition it was decided that a photograph of cold sores was a useful adjunct to those not quite clear what a cold sore was - although most appeared to be, when this was described. Other words in the questionnaire were expanded upon to clarify what was meant by for example 'depression' (see questionnaire - Appendix 1a). Although some 'jargon' words were left in the questionnaire as a concession to brevity for example the word 'migraine', it was apparent from piloting that a careful history was also needed. Certain types of wording were more ambiguous than others.

After administering the first 3 or 4 case questionnaires a number of modifications were introduced. These were as follows:-

- 1) to include a work address where relevant to help in considering cases of contact with other Bell's palsy patients and to serve as a reminder to ask about social contacts.
- 2) the order of questions 2 and 3 were changed as a complementary question 2a was also asked.
- 3) The words 'prior to the facial weakness' were dropped from question 6 and this was reworded 'Have you noticed things taste differently?'
- 4) The doctors 'correction' for question 15 about emotional strain (a parallel set of boxes) was dropped and subsequently the S.R.E. check list was introduced.

As regards repeatability of the questions (or level of agreement between replicate responses) it was apparent from piloting that the questions about cold sore history produced most difficulty with anamnesis. Expert advice was sought but it was felt that because of the use of controls, and with supplementation from serology studies it was not necessary to formally assess the repeatability of these questions.

8.4.2 Features of the case questionnaire design and content

The questionnaire was designed to unambiguously and efficiently collect relevant data about the natural history of Bell's palsy - with particular emphasis on exposure to herpes simplex virus and various biological stressors associated with recrudescence and reactivation. Wherever possible the patient was asked to recount his or her story in their own words first. The questionnaire comprises a set of specific questions designed for use by an interviewer, with elaborations and answers to open questions recorded in the margin and at the end of the questionnaire under 'comments'.

8.4.3 The control questionnaire

This was modified in a way in keeping with the general aims of the case control study whilst being divested of inappropriate questions relating to specific aspects of the features of facial paralysis. Further modification was required for the questions on exposure to alcohol and sunlight, where because Bell's palsy patients were on average recalling events just prior to a significant event (the onset of the palsy) on average two to three weeks previously, it was felt no equivalent question was possible for controls but in order to determine the likely exposure to alcohol or sunlight as near accurately as possible the previous 24 hours were used, thus introducing a bias.

A number of questions on the control questionnaire also involved rephrasing in a manner appropriate for well rather than ill people, and this difference in state has also to be borne in mind in interpretation of the results.

8.4.4 S.R.E. (Schedule of Recent Events) check list

Although Bell's palsy and stress have been studied the S.R.E. check list has not been used before. This questionnaire attempts to assess

more objectively the degree of stress individuals are under. A number of studies have examined recent life events and illness (Holmes 1967; Connolly 1985; -Cooke 1985, Walker 1988). Perhaps the main objection to these questionnaires is the fact that the meaning of the events or the significant impact to the individual is not explored by such quantitative evaluation. Furthermore the life events schedule was developed as a questionnaire and not as a self-administered check list as used by the author. Nonetheless the use of controls and the clear onset in time of the facial paralysis make this information a useful supplement to the questionnaire information. The different time periods involved also have to be taken into consideration (6 months S.R.E., 1 month questionnaire) when examining the results.

This check list was self administered after a short explanation by the author and took on average 3 to 5 minutes to complete. An administrative problem resulted in the S.R.E. only being used 2-3 months into the study when some cases had already been interviewed and 'missed' so that S.R.E. scores became available for 54 cases and 80 controls.

8.4.5 Validity of the questionnaires

The validity or extent to which the questionnaires measure what they purport to measure can be assessed by indirect methods. The term validity implies a 'gold standard', and this is not available for symptoms.

Many of the questions have been derived from what convention has shown to be the best. A number of questions used are very similar to those used by Mr Murray (The Edinburgh Royal Infirmary Bell's palsy questionnaire). Furthermore the questionnaire was also shown to two North Manchester consultants for their comments and assessment.

Some of the questions e.g. on skin-type, relating to reactions to the sun, however, had not been independently assessed. In piloting the questionnaire on patient volunteers, ease or difficulty in answering such questions sometimes resulted in modification of the wording of the question. It has already been mentioned that the most ambiguous or difficult questions in the questionnaire related to previous exposure of HSV and cold sore history. These questions were largely based on Grout's epidemiological survey of cold sores (1976).

A tendency to over or underreporting could be assessed by checking responses of cases and controls, with the incidences or prevalences of diseases known to be associated, or lacking an association, with Bell's palsy. Some questions were validated by finding an expected correlation e.g. between the S.R.E. stress score, and responses to the questions on emotional strain and depression (see results discussion p.165).

The main method of validation was however by clinical assessment by the author and this is discussed further under "observers in the study". Further independent sources of information were from GP's records over medication when this was in doubt, and from consultant letters to GP's, where available.

The problem of subjectivity in reporting is inevitable in this type of study but by comparison with controls any systematic bias should be reduced.

8.4.6 Administration of the questionnaires (case and control)

For 78 patients and all controls the interviews took place in the home. 2 patients however were interviewed at work. 1 patient moved house and had to be contacted through FPC records. Several patients required more than one visit to find them in, despite letters agreeing a convenient time. One patient in Oldham was finally contacted and interviewed after 4 visits.

The questionnaires took on average 30-40 minutes to complete for cases (which included an examination) and 15 minutes for controls. Before proceeding with the questionnaire the interviewer spent about 5 minutes or so in general conversation, in order to establish a good rapport with the respondents.

CHAPTER 9

Methods II

Processing Data, Computing and Statistics

9.1 Data Processing

In accordance with general communication theory, data has to be handled or grouped in meaningful ways as information, before it can be processed as knowledge. The data sets incorporated into the design of the questionnaires come under 2 main categories:-

			<u>Cases</u>	<u>Controls</u>
1)	Documentation of clinical features of interest in Bell's palsy - history, examination, outcomes		+	-
2)	Aetiological data	a) general - preceding exposure to a variety of aetiological agents	+	+
		b) specific- biological "stressors" of relevance to Adours and extended hypothesis	+	+
		- HSV history and exposure	+	+

Furthermore the data was collected such that should sufficient be collected, prognostic theories could be tested e.g. pain, pregnancy, age, taste, diabetes, etc. with outcomes e.g. poor recovery from the paralysis.

The questionnaires were designed to look primarily at possible aetiological factors rather than to assess unfavourable outcome; nonetheless cross tabulations and multivariate analysis were performed on many of the data sets relating clinical outcome to proposed aetiologies or clinical features.

9.2 Coding

Coding of the case and control data was performed by the author and checked before entering on the computer. 75 separate responses and data were collected as a maximum per case questionnaire and 59 for controls.

9.3 Computing

The coded data was entered onto the mainframe IBM Nottingham University computer using SPSS X. From this much information about frequencies was obtained. Chi square tests were performed on case control data as were cross tabulations and multivariate analysis examining aetiologies and outcomes.

It subsequently became necessary to transfer this information to Southampton University's IBM computer and this was achieved through J.A.N.E.T. The author was subsequently involved in matching code numbers such that match pair analysis could be performed.

Computing and statistics materials

SPSS^x, Version 2.2. SPSS Europe BV, The Netherlands.

Minitab, Release 5.1. Minitab Inc. CLE.COM Ltd, England.

Microsoft Chart. Microsoft Corporation, 1987. US and Canada.

Hardware: IBM 3090-150 mainframe computer.

9.4 Case Control Study Methods

All cases and controls were matched for age by decade, sex, and social group (upper, middle and lower). McNemar tests (with correction for continuity) were applied to case-control match pair data. The results on which the analyses were applied were constructed as follows:-

	Controls	
	Yes	No
Yes		
Cases		
	No	

Of the 80 case pairs on reviewing the information 1 was noted to be mismatched in terms of social group, differing by more than one group. For specific analysis e.g. skin-type further exclusions were made e.g. all 8 non-caucasian cases were not matched. In this instance n was 71.

Results are presented in terms of numbers of cases or controls, percentages of cases or controls chi square, (with continuity correction), d.f., p values and 95% confidence intervals.

9.5 Statistics Used

Chi-square tests (χ^2)

All Chi-square tests were performed with Yate's continuity correction factor. 95% confidence intervals (CI) were calculated for the difference between the two population proportions (Gardner and Altman, 1989).

Mann-Whitney U test (M-W)

95% confidence intervals for the differences in population medians (Campbell and Gardner, 1988) are also calculated for this non-parametric test.

Non-parametric correlation

A Spearman rank correlation is used to correlate duration of paralysis with age.

Results of Epidemiological Studies

DESCRIPTIVE STUDY

Table 6: Response to Letters per F.P.C. Area

F.P.C. area	Letters distributed to G.P's		Response (positive) to first letter		Response to second letter	
	No.	%	No.	%	No.	%
Bolton	130	11.2%	23	9.1%	18	12.5%
Bury	86	7.7%	27	10.7%	17	11.8%
Rochdale	100	8.9%	27	10.7%	23	16%
Salford	170	15.2%	29	11.5%	15	10.4%
Manchester	280	25%	52	20.6%	25	17.4%
Oldham	115	10.3%	22	8.7%	18	12.5%
Stockport	140	12.5%	41	16.2%	18	12.5%
Tameside	100	8.9%	31	12.3%	10	6.9%
TOTAL	1,121	100%	252	100%	144	100%

Respondents to first letter 252 G.P's or 22.5% of Greater Manchester G.P's

Respondents to second letter 144 G.P's - a response rate of 57%

(12.8% of Greater Manchester G.P's).

10.1 Study Incidence

Denominator information and 'corrections'

Using the information from the more consistently responding G.P's at 8 months. (Appendices 3b, 3c).

The total list size at 8 months = 361,111

Analysing the G.P. responses to the second letter:-

121 gave personal list sizes

15 gave shared list sizes:

{ 15 reporting G.P's
21 non-reporting G.P's

8 gave no list size

—
Total 144

mean list size = 2,200 (FPC information).

Correction of denominator for 8 missing lists = 378,711

This figure includes partners lists from which cases may have been reported.

Known total shared list size = 77,850

Case reporting

The number of cases of Bell's palsy reported over 1 year by the 144 more consistently responding G.P's = 62 cases

56 cases on the list of a participating G.P

6 cases from the list of a non-participating G.P

Thus, 7.7% of cases came from a non-reporting G.P's list.

This figure is comaprable with the percentage of the total denominator which known non-reporting G.P's list constitute:-

$$\frac{77,850}{36} = \text{mean list size } 2162.5 \text{ per shared list G.P.}$$

21 non-reporting G.P's total list estimated at 45,412.5

Therefore, percentage of total denominator known to include

$$\text{non-reporting G.P's patients} = \frac{45,412.5}{378,711} \times \frac{100}{1}$$

or 12%

The most accurate estimate of the study incidence remains therefore:

$$\frac{62}{378,711} \text{ per year}$$

or

$$\frac{16.4 \text{ cases of Bell's palsy per } 100,000 \text{ population per year.}}{}$$

However, this figure is likely to be a considerable underestimate - see discussion.

Geographical Distribution of Cases

See A3 Pull-out Ordnance Survey Map of Greater Manchester (back page).

10.2 Descriptive Study Results - Figures and Tables

Fig. 10.1 Reported Incidence of New Cases of Bell's Palsy per month
of the Study Period

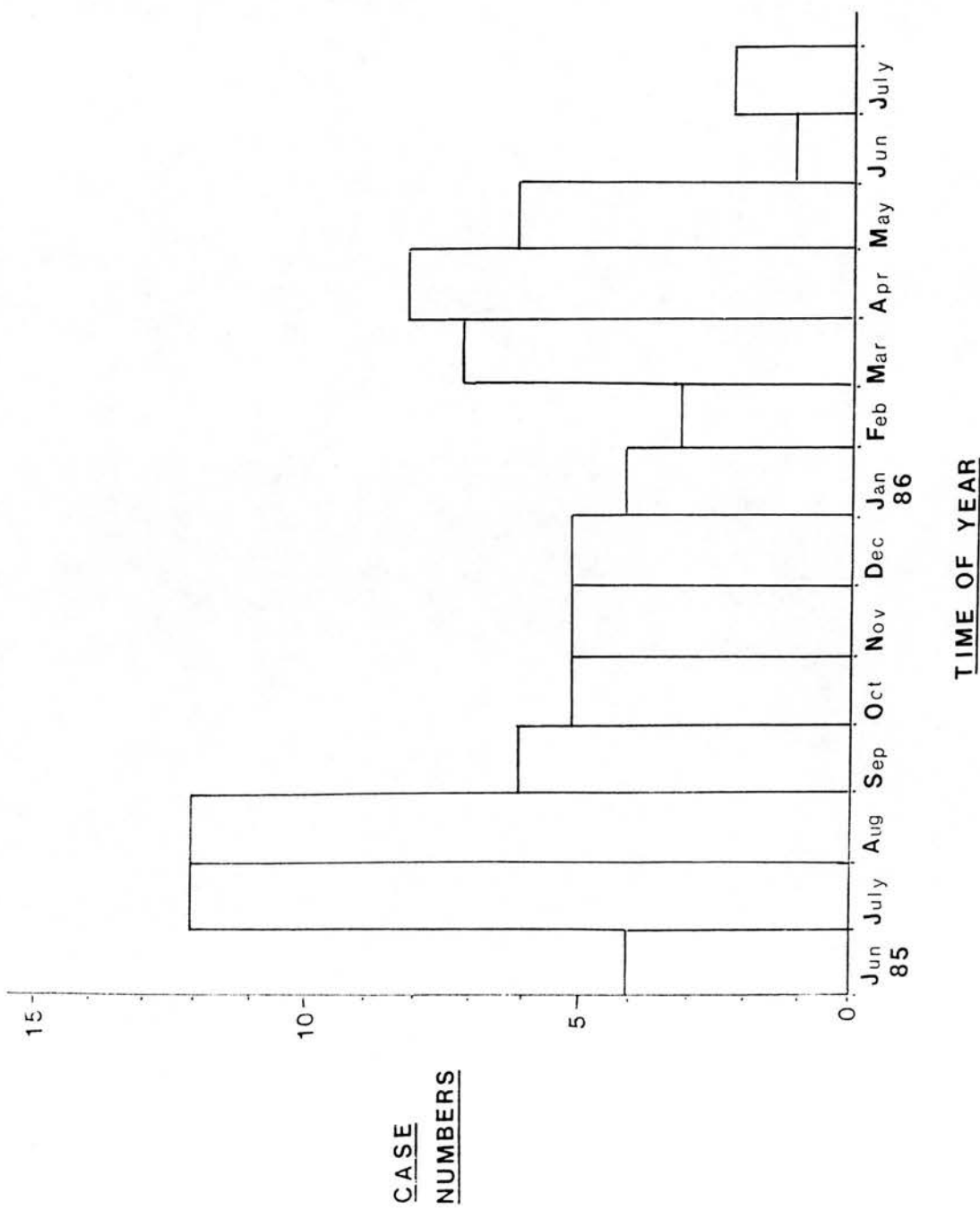


Fig. 10.2: Age Distribution of Cases

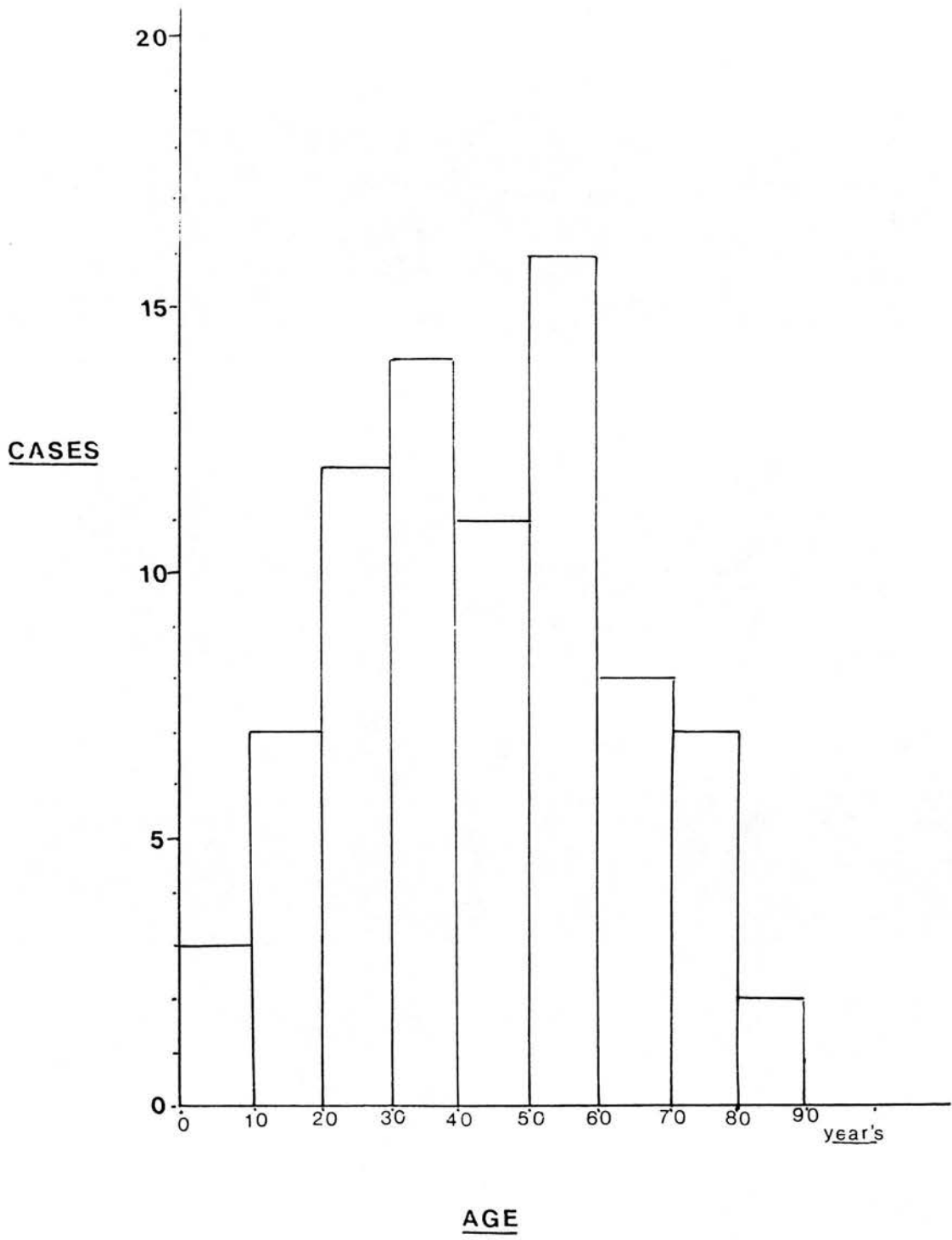


Table 7: % of cases of Bell's palsy in different age groups and
% of G.M. population by age compared (1981 OPCS)

<u>Age group</u>	<u>Population by age</u> <u>Greater Manchester</u>	<u>Bell's palsy</u> <u>% of cases by age</u>
0 - 4	6.2%	1.25%
5 - 15	16.9%	8.75%
16 - 24	14.4%	7.5%
25 - 34	14.2%	18.75%
35 - 44	11.8%	18.75%
45 - 60 (♀) or 65 (♂)	19.3%	30%
60 (♀) 65 (♂) - 75	17.3%	8.75%
75+ { ♂	1.6%	0%
{ ♀	3.8%	6.25%

Fig. 10.3: Age distribution of cases and Greater Manchester population

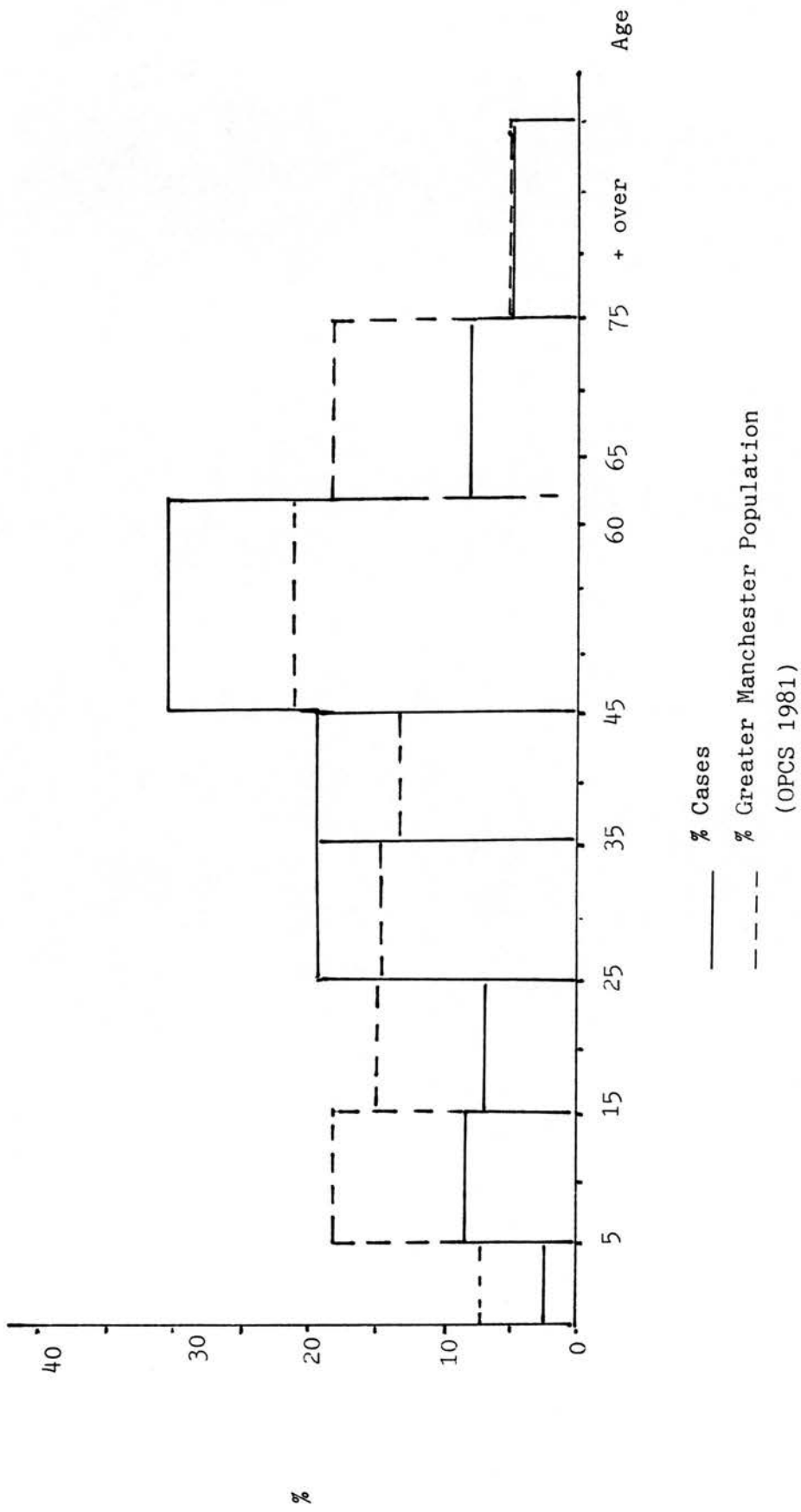
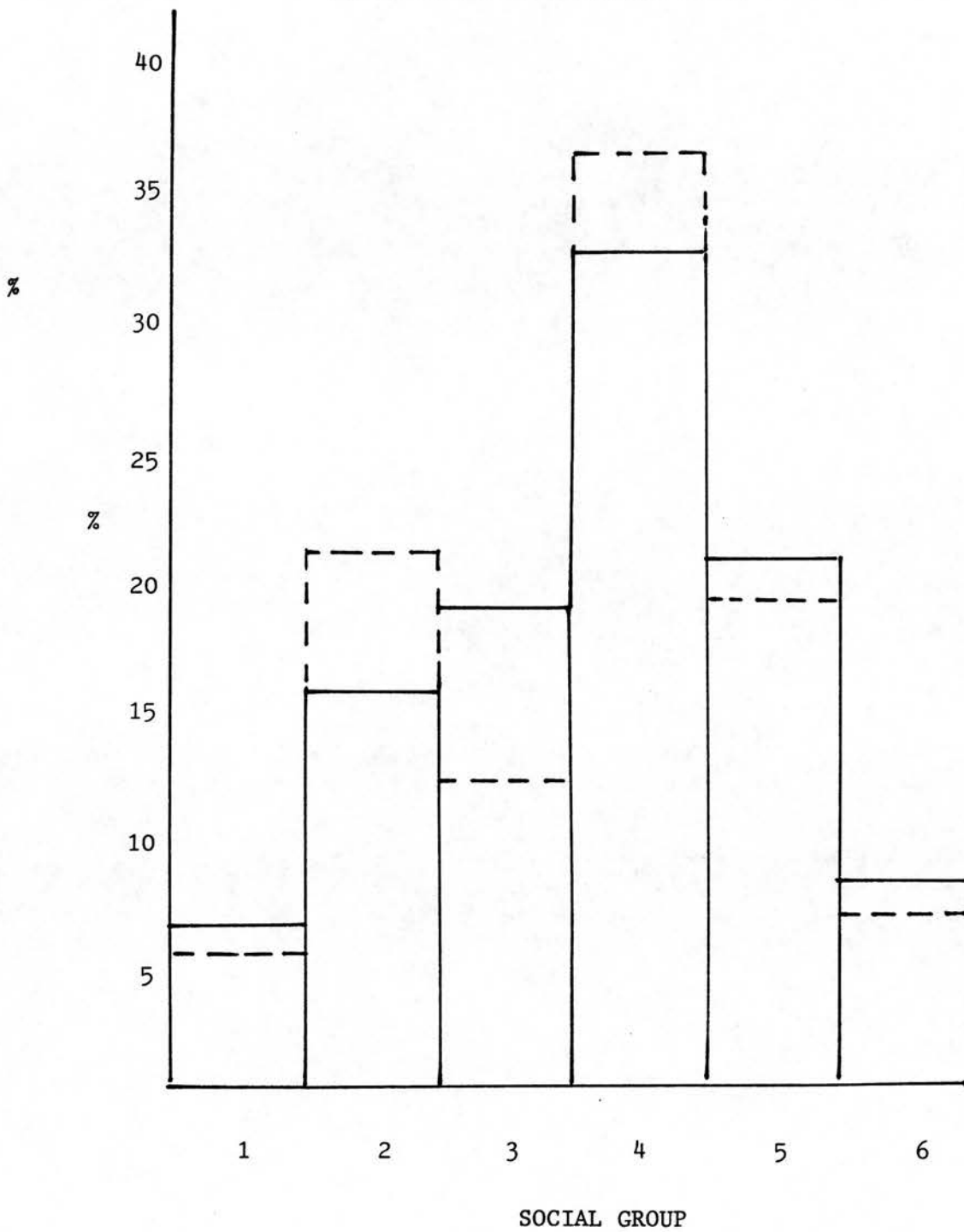


Table 8: % of cases of Bell's palsy in different social groups and
% of economically active G.M. population by social group
compared

<u>Group</u>	<u>No. of cases</u>	<u>% cases</u>	<u>% economically active Greater Manchester population</u>
1	5	6.4	5.2
2	12	15.4	21.4
3 (3n)	14	17.9	12.1
4 (3m)	25	32.0	36.5
5	16	20.5	18.1
6	6	7.7	6.7
7 (unemployed 1 yr.)	(2)	-	-
TOTAL:	78(80)	100%	100%

(figures in last column obtained from OPCS 1981 survey).

Fig. 10.4: Social group distribution of cases and
Greater Manchester population



— % cases in each Social Group

- - - % of Greater Manchester population
in each Social Group (OPCS 1981)

Table 9: Sex incidence

male	35
female	45

Ratio : of 1:13. m:f

Table 10: Ethnic origin

Caucasian	72
Indian	5
Negroid	1
Chinese	1
Arabic	1

CLINICAL FEATURESInterval before review (by the author)

35% of cases seen within 10 days

50% of cases seen at 2 weeks

95% of cases seen within 3 months from the onset of the palsy.

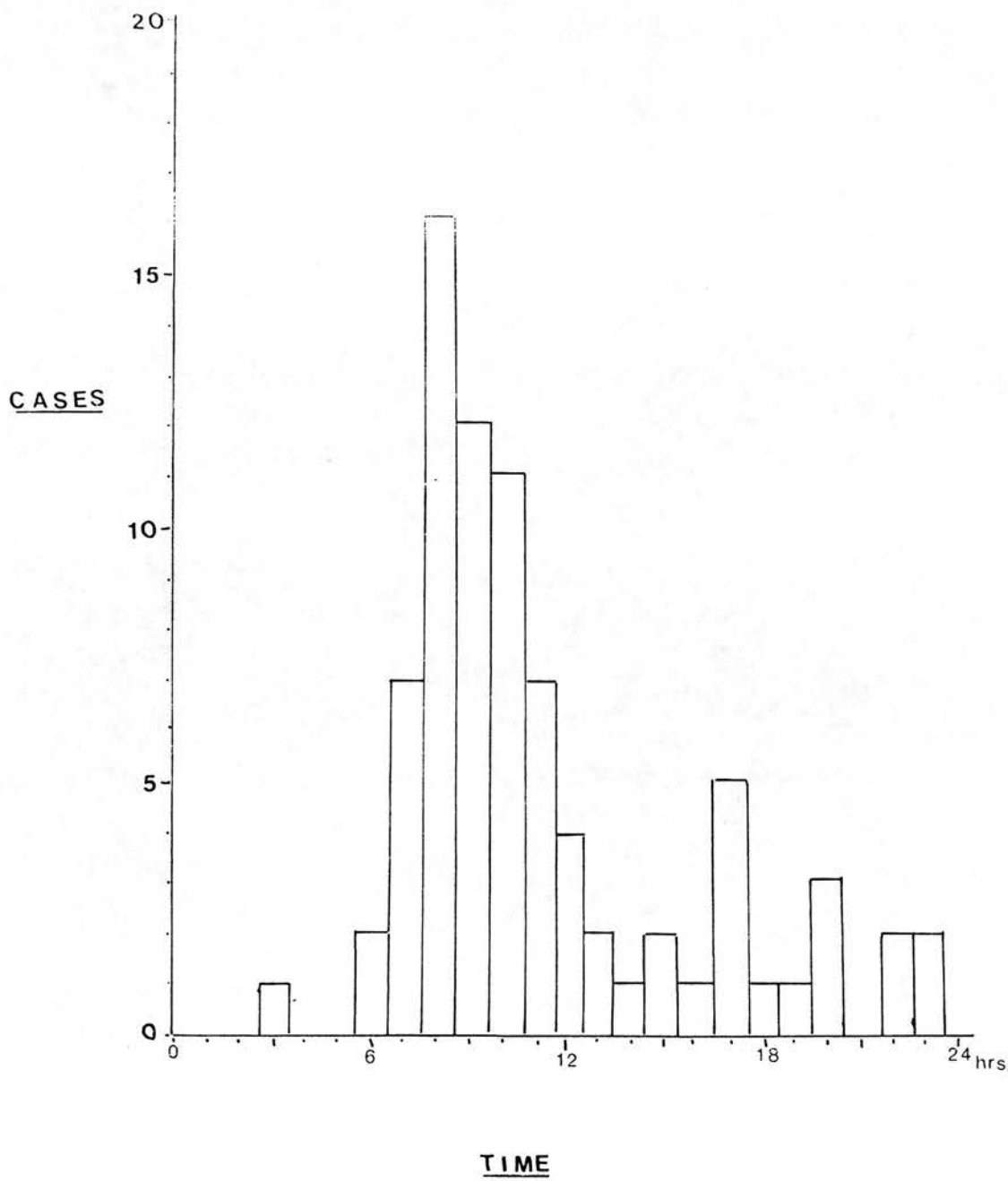
Table 11: Side involved and bilateral palsy

Right	39 cases (48.7%)
Left	41 cases (51.2%)
Bilateral	0 cases

History of recurrent palsy

recurrent palsy 3 cases or 3.75%

Fig. 10.5: The hour of day facial weakness first noted



56 or 70% occurred during first 12 hours of day

24 or 30% occurred durring second 12 hours of day

Table 12: Day of onset of facial weakness with respect to the menstrual cycle

Day of onset in the cycle

	<u>Days 1 - 14</u>	<u>Days 15 - 28</u>
	2 cases day 2	2 cases day 21
	1 case day 4	1 case day 27
	1 case day 5	
	1 case day 6	
	1 case day 7	
	2 cases day 10	
	1 case day 14	
Total	9	3

(no cases occurred after day 28 in longer cycles)

Table 13: Pregnancy and puerperium

	1st trimester	2nd trimester	3rd trimester	puerperium
cases	0	1	2	2

Total: 5 cases

Table 14: Clinical indication of speed of onset

from normal to noticeable weakness of face

	<u>No. of cases</u>	<u>%</u>
6 hours	20	31.7
6-12 hours	28	44.4
12-24 hours	5	7.9
Days	10	15.9
TOTAL	63	100%

(Unable to say)

17

ASSOCIATED SYMPTOMSTable 15: Symptom reporting in Bell's palsy patients

<u>Symptom</u>	<u>Response Cases</u>			<u>Response Controls</u>
Auricular pain	38 42	yes no	(47.5%) (52.5%)	controls 1 yes (1.31%)
Occipital headache	13 67	yes no	(16.3%) (83.8%)	controls 0 yes
Auricular rash	0 80	yes no	(100%)	controls 2 yes (2.5%)
Dry eye	9 71	yes no	(11.3%) (88.8%)	controls 0 yes
Hyperacusis	9 71	yes no	(11.3%) (88.8%)	controls 0 yes
Right facial numbness	11 69	yes no	(13.8%) (86.3%)	controls 0 yes
Left facial numbness	20 60	yes no	(25%) (75%)	controls 1 yes (1.3%)
Both sides - total (facial numbness)	31		(38.8%)	
Hoarseness	0 80	yes no	(100%)	controls 5 yes (6.3%)
Vertigo	4 76	yes no	(5%) (95%)	controls 5 yes (6.3%)
Burning sensation of face	7 73	yes no	(8.8%) (91.3%)	controls 3 yes (3.8%)
Alteration of taste	32 48	yes no	(40%) (60%)	controls 1 yes (1.3%)

(Primarily descriptive but control information included for interest)

Fig. 10.6: Symptom reporting in Bell's palsy patients

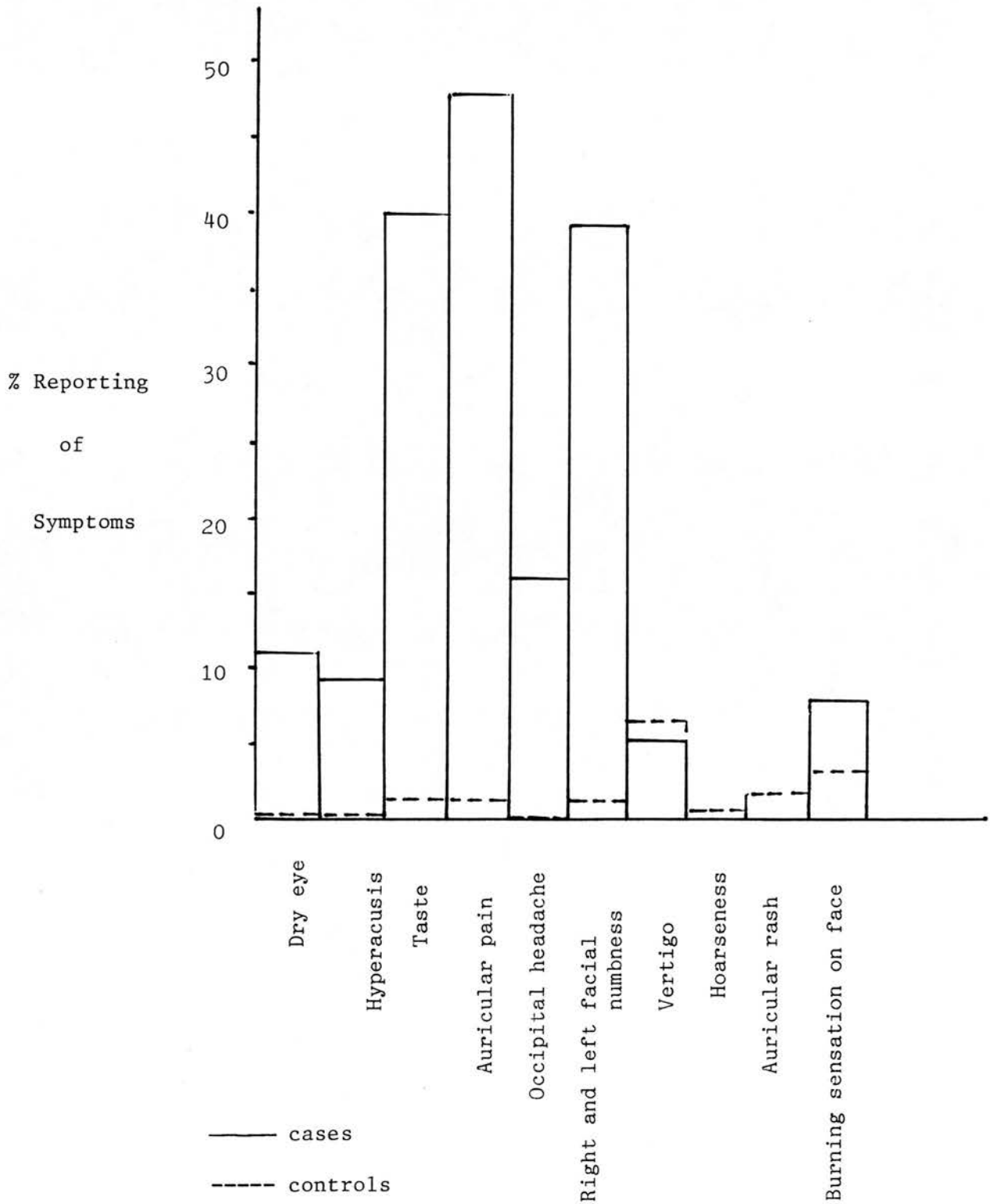


Table 16:

(a) Taste alteration

(noted in 30 or 37.5% of cases)

When noted compared to onset of facial weakness

a)

<u>Timing</u>	<u>Cases Numbers</u>	<u>Cases %</u>
a) Several days before	10	33.3
b) 12-24 hours before	7	23.3
c) 6-12 hours before	2	6.7
d) 0-6 hours before	1	3.3
e) at the time of onset	3	10
f) 0-6 hours after	2	6.7
g) 6-12 hours after	1	3.3
h) 12-24 hours after	2	6.7
i) Several days after	1	3.3
Unable to say	1	3.3
<u>TOTAL</u>	<u>30</u>	<u>100%</u>

Table 16:

(b) % of those giving a history of taste disturbance (n = 29)
in relation to the onset of facial weakness

b)

Before onset (a, b, c)	65.6%
Approximately coincidental (d, e, f)	20.7%
After onset (g, h, i)	13.8%

HOSPITAL REFERRAL

15 cases or 18.75%.

Examination findingsTable 17: Diminished pin prick sensation to face (5th nerve)

Right side	5 cases	6.25%
Left side	7 cases	8.75%
TOTAL	12 cases	15%

No abnormality of the palatal reflex was found in any case (test of 9th cranial nerve).

Inspection of the vocal cords was only possible because of the nature of the study in two patients seen for follow up in the university department of general practice. No abnormality of movement or position of the cords was noted.

Permission for blood to be taken was obtained in 46 cases - see antibody results (p.120).

The urine was tested in 43 patients by dipstix method. 8 out of 43 or 18.5% had glycosuria.

Features of the facial paralysisTable 18: Gradation of paralysis

Of 80 patients giving a clear history of a sudden onset of facial weakness the gradation was assessed as follows:-

56 cases	70% partial
24 cases	30% complete

Table 19: Examination of facial paralysis

50 cases (62.5%)	significant residual weakness
30 cases (37.5%)	less than 10% loss of power or early recovery

26 right sided : 24 left sided cases of facial weakness

Facial Nerve Recovery:Severity and duration of paralysisResponse to letter at 6 months - see appendix 2e

47 out of 80 patients responded (59% response rate)

Table 20: Facial nerve recovery - (letter)

complete recovery	33
incomplete recovery	12
unable to interpret	2
TOTAL	47

Of 33 non-responders, information was already available from the interview and examination, and 15 were known to have made a complete recovery. The remaining 18 were then telephoned for missing information. The results of the telephone enquiry were:-

Table 21: Facial nerve recovery - (telephone enquiry)

complete recovery	12
incomplete recovery	1
unable to say or not contactable	5
TOTAL	18

It was possible to look for agreement between the letter and examination for those recorded incomplete recovery by letter (2 false negatives with examination as the gold standard). Because a further examination was not carried out at the same time as the letter the number of false positives could not be determined.

Table 22: Facial nerve recovery at 6 months

complete recovery	60 (82%)
incomplete recovery	13 (18%)
TOTAL	73

Missing information - 7 patients

The reported disability at 6 months were as follows for 13 patients stating incomplete recovery.

Table 23: Residual problems at 6 months

7	loss of power
5	abnormal facial movements
8	abnormal hearing
1	impaired taste
5	abnormal loudness of sound

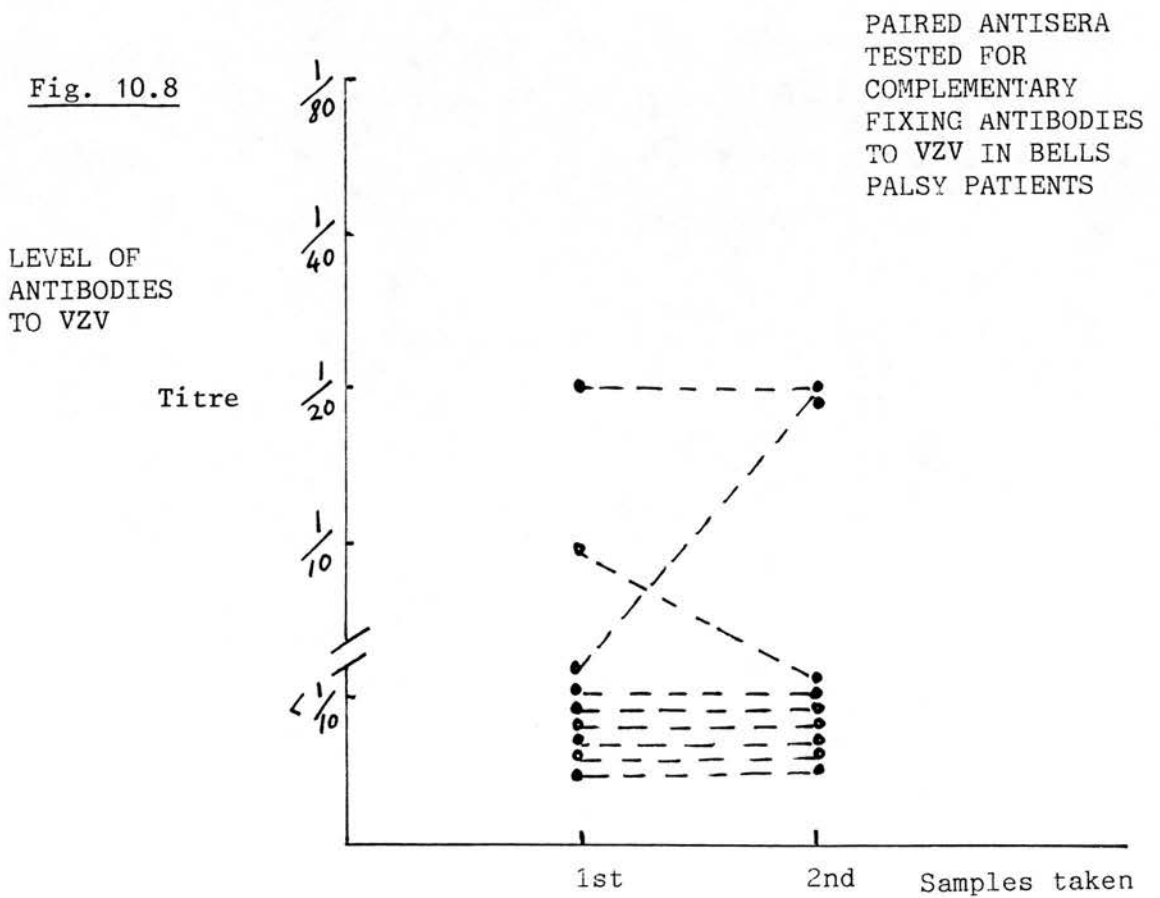
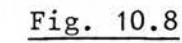
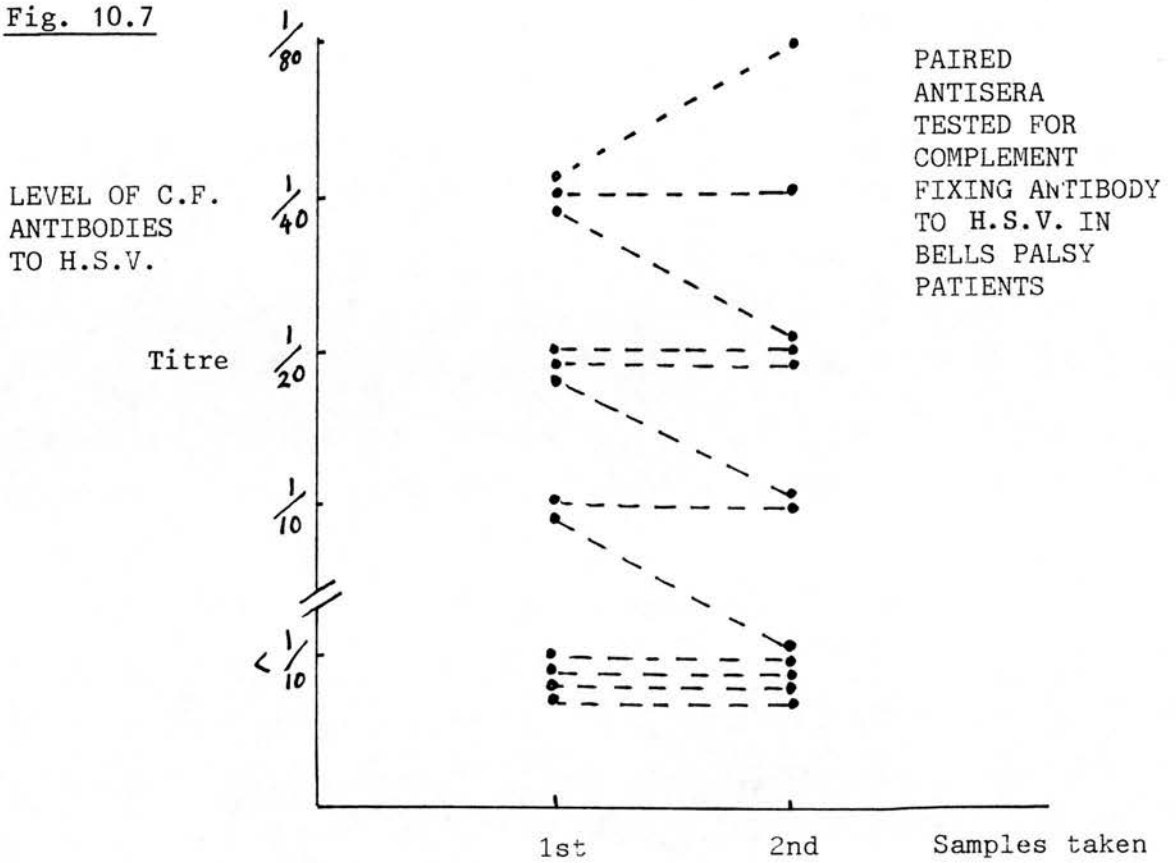
At 18 months, 2 were reported to have continued facial weakness to a significant degree.

10.3
Antibody Study
Results

Table 24, Part I: C.F. fixing antibodies to HSV, VZV and other viruses in Bell's palsy cases

No	Sex	Age	HERPES SIMPLEX VIRUS			VARICELLA-ZOSTER			OTHER			
			Sample 1 Date	Titre	Sample 2 Date	Titre	Sample 3 Date	Titre	Sample 1 Date	Titre	Sample 2 Date	Titre
2	M	29	27/6/85	1/10								
8	M	13	3/7/86	1/10								
9	F	64	3/7/86	1/40								
5	M	40	21/11/85	1/10								
6	M	72	18/12/85	1/10								
18	M	24	18/7/85	1/10								
15	F	50	11/10/85	<1/10								
17	M	39	8/7/86	1/40								
19	F	31	23/3/86	<1/10	3/4/87 15							
20	M	44	20/9/85	1/20	4/10/85 34							
24	M	55	10/7/86	1/80								
21	F	77	6/3/86	1/10								
25	M	18	11/7/86	1/80								
22	M	40	4/2/86	1/10								
27	M	64	5/9/85	1/10								
26	F	56	11/10/85	1/10	21/10/85 13							
28	F	87	18/10/85	1/10								
32	F	10	15/7/85	<1/10								
29	F	53	24/9/85	1/20								
37	M	39	1/7/86	1/20								
36	M	54	15/8/85	1/40	2/9/85 24							
37	M	37	3/7/85	<1/10								
38	M	20	15/7/85	<1/10								
40	F	48	15/7/86	1/80								
42	M	38	8/8/85	<1/10								
45	F	35	29/7/85	1/10								
46	M	62	30/9/85	1/40	14/10/85 15							
51	F	71	5/7/85	<1/10	27/10/85 28							
80	M	15	2/10/85	<1/10	15/10/85 17							
49	F	54	15/11/85	1/10	3/12/85 27							

Fig. 10.7



10.4 Case Report

A 31 year old female patient was given the Sabin oral polio vaccine and she noted at once a burning sensation in the left half of her tongue which persisted for over a week. She noted also that taste was altered after taking the drops and this persisted for several days.

47 hours later she developed a complete left sided facial paralysis which became noticeable several hours after waking. Just before the weakness developed she noted a patch of circumoral numbness on the left side. Subsequently this spread to involve the entire left side of her face. After the onset of the weakness the patient also noted abnormal loudness of sound and pain within the ear.

The patient was seen and examined 72 hours after the onset of the palsy when a complete left lower motor neurone lesion of the seventh nerve was noted. In addition there was objective diminution to pinprick and light touch sensation over the territory of all 3 divisions of the left 5th cranial nerve and a diminished corneal reflex on that side. The patient had a normal gag reflex and otherwise normal examination.

There was no family history of facial paralysis or of diabetes. The patient herself was not diabetic. There had been no preceding U.R.T.I or recent evidence of HSV infection.

At 6 months having been treated solely with physiotherapy the outcome was of residual paralysis with approximately 60% recovery of movement. There was synkinesia and also crocodile tears.

A sample for antibody studies was taken during the convalescent period and showed 1/80 to polio type I but no other titres were raised (HSV, VZV).

This case report is an interesting association between facial paralysis and taking Sabin vaccine. Previous reports to the C.S.M. include 1 optic neuritis, 1 encephalitis, 1 dizziness, 2 meningitis, 2 "paralysis" and 4 flaccid paralysis and 1 auditory vestibular tinnitus, but no facial paralysis.

Facial diplegia is known to occur during polio epidemics as part of a bulbar palsy. May speculated that the ascending route of infection, i.e. via the chorda tympani nerve is the principal route of entry of virus in cases of Bell's palsy. The virus travelling at a rate of 2mm hour (slow axonal transport) would however probably take 2 days to reach the geniculate ganglion and longer than this to reach the brain stem. The early symptoms represent 5th nerve involvement as well as the chorda tympani (taste pathways).

Both burning and taste disturbance were experienced immediately. It is of some interest then that the patient went on to develop an objective 5th and 7th nerve weakness on the corresponding side only 48 hours later. It is known that viraemia following the polio vaccine does not usually occur until the 9th day. Thus the vaccine may have acted by producing a "multifocal" reactivation of another virus rather than being directly responsible for the nerve injuries itself although serological support is lacking for this assertion. Alternatively the burning might have represented a contaminant but this had not been reported to the C.S.M.

Fig. 10.9. Key

1.

2.

3.

4.

Clinical features of a left lower motor neurone facial lesion.

- 1) Face at rest
- 2) Smiling - lower divisions affected
- 3) Frowning - anterior belly of occipitofrontalis affected
- 4) Eye closure - weakness of orbicularis oculi



10.5

RESULTS OF CASE-CONTROL STUDY

GENETIC FACTORSTable 25: Positive family history of Bell's palsy

<u>Relative</u>	<u>Cases</u>	<u>Controls</u>
<u>1° relatives</u>		
Parent	2	0
Child	4	1
Sibling	3	0
<u>2° relatives</u>		
Grandparent	0	0
Other relatives	4	0
Total Relatives	13	1

chi square 5.82 d.f. 1 p 0.02 95% C.I. 0.03, 0.20

Numbers of cases with a positive family history 11 or 13.8%

Number of controls with a positive family history 1 or 1.3%

Of the affected relatives of cases:-

9 or 69.2% were first degree

4 or 30.8% were second degree

DIABETES

Individuals giving a personal history of diabetes.

3 cases, 3.8% non-insulin dependent type

0 controls

Table 26: Positive family history of diabetes

<u>Relative</u>	<u>Cases</u>	<u>Controls</u>
<u>1° relatives</u>		
Parent	4 (N), 1 (I)	4 (N), 3 (I)
Child	1 (N)	1 (N)
Sibling	0	0
<u>2° relatives</u>		
Grandparents	3 (N), 1 (I)	6 (N)
Other relatives	3 (N), 3 (I)	2 (N)
Total relatives	16	16

A separate history of insulin dependent or non-insulin dependent diabetes was recorded. (N) = non-insulin dependent, (I) = insulin dependent).

Number of cases with a positive family history of diabetes, 15 or 18.81%

Number of controls with a positive family history of diabetes, 14 or 17.51%.

Of affected relatives:-

1st degree relatives 6 cases, 43% and 8, 57% controls

2nd degree relatives 10 cases, 56% and 8, 44% controls

PAST MEDICAL HISTORYTable 27

<u>Condition</u>	<u>Cases</u>	<u>Controls</u>	<u>chi-</u> <u>square</u>	<u>df</u>	<u>p</u>	<u>95% C.I</u>	
Pancreatitis	0	0	-	-	-	-	-
Menières disease	1 (1.3%)	1 (1.3%)	0.50	1	0.48	-	-
Migraine	10(12.5%)	13(16.25%)	0.21	1	0.65	-0.15	0.07
Schizophrenia	0	0	-	-	-	-	-
Asthma	2 (2.5%)	6 (7.6%)	1.12	1	0.29	-0.13	0.02
Drink problem	0	0	-	-	-	-	-
Heart trouble	4 (15%)	2 (2.5%)	0.00	1	1.00	-0.04	0.0
Endocrine, e.g. thyroid	0	7 (8.9%)	-	-	-	-	-
Rare endocrine disease	0	0	-	-	-	-	-
Genital herpes	0	0	-	-	-	-	-
Mouth ulcers	10(12.5%)	25(31.6%)	6.76	1	0.01	-0.34	0.0
Hypertension	12(15%)	5 (6.3%)	2.12	1	0.145	-0.01	0.20

Drug history

Diuretics - 7 cases, 2 controls; tablets for arthritis - 3 cases, 4 controls;

Analgesics - 0 cases, 0 controls; pentazocine, 0 cases, 0 controls;
chlorpropamide, 0 cases, 0 controls.

Table 28: Alcohol consumption/preceding exposure

Alcohol consumption 24 hours before onset of facial weakness - cases
 Alcohol consumption previous 24 hours - controls.

		<u>Cases</u>	<u>Controls</u>
Alcohol consumed	YES	9 (11.3%)	29 (36.3%)
	NO	69 (86.3%)	51 (63.8%)

chi-squared 12.00 d.f. 1 p < 0.001 95% C.I - 0.39, -0.11

Table 29: Smoking habits

		<u>Cases</u>	<u>Controls</u>
	YES	31 (38.8%)	22 (27.8%)
	NO	49 (61.2%)	57 (62.2%)

chi-squared 1.73 d.f. 1 p 0.19 95% C.I -0.04, 0.28

Table 30: Nailbiting

	<u>Cases</u>	<u>Controls</u>
with habit	22 (27.5%)	20. (25%)

chi-squared 0.03 d.f. 1 p 0.86 95% C.I -0.12, 0.17

Table 31: Non-specific or upper respiratory tract infection in previous 2 weeks

<u>Symptoms</u>	<u>Cases</u>	<u>Controls</u>	<u>chi-squared</u>	<u>d.f</u>	<u>p</u>	<u>95% C.1</u>
an illness with a temperature	18 (22.5%)	4 (5.1%)	6.86	1	0.01	0.05, 0.29
A cough, cold or chest infection	25 (31.3%)	10 (12.7%)	4.97	1	0.03	0.03, 0.31
a sore throat	20 (25.0%)	9 (11.0%)	4.76	1	0.03	0.03, 0.26

Table 32: Exposure to draught

	<u>Cases</u>	<u>Controls</u>
YES	12 (15.0%)	6 (7.5%)

chi-squared 0.64 d.f.1 p 0.42 95% C.1 -0.04, 0.15

Table 33: Exposure to cold or chilling

	<u>Cases</u>	<u>Controls</u>
YES	6 (7.5%)	2 (2.5%)

chi-squared 1.50 d.f. 1 p 0.22 95% C.1 -0.01, 0.11

Table 34: Increased physical strain or work

(in 2 weeks prior to facial weakness cases - or previous 2 weeks controls).

	<u>Cases</u>	<u>Controls</u>
YES	9 (11.3%)	3 (3.8%)

chi-squared 2.08 d.f. 1 p 0.15 95% C.1 -0.01, 0.17

Table 35: Exposure to bright sunlight

(24 hours prior to onset of facial weakness - cases
previous 24 hours, controls).

	<u>Cases</u>	<u>Controls</u>
YES	6 (7.5%)	2 (2.5%)

chi-squared 1.12 d.f. 1 p 0.29 95% C.I. -0.02, 0.12

Table 36: Skintype

<u>Type</u>	<u>Cases</u>	<u>Controls</u>
Burn	33 (46.5%)	17 (21.5%)
Burn > Tan	13 (18.3%)	17 (21.5%)
Tan > Burn	7 (9.9%)	23 (29.1%)
Tan	18 (25.9%)	22 (27.8%)

chi-squared 7.50 d.f. 1 p 0.01 95% C.I. 0.08, 0.41

Table 37: Recent history - previous 3 months, of depression

	<u>Cases</u>	<u>Controls</u>
YES	16 (20.3%)	3 (3.8%)

chi-squared 8.47 d.f. 1 p < 0.01 95% C.I. 0.07, 0.28

Table 38: Emotional strain in preceding month - subjective assessment

<u>Amount of strain</u>	<u>Cases</u>	<u>Controls</u>
less than normal	1 (1.3%)	4 (5%)
normal	40 (50.6%)	59 (73.8%)
more than normal	24 (30.4%)	13 (16.3%)
much more than normal	14 (17.7%)	4 (5%)

chi-squared 9.76 d.f. 1 p < 0.01 95% C.I. -0.44, -0.11

Fig. 10.10

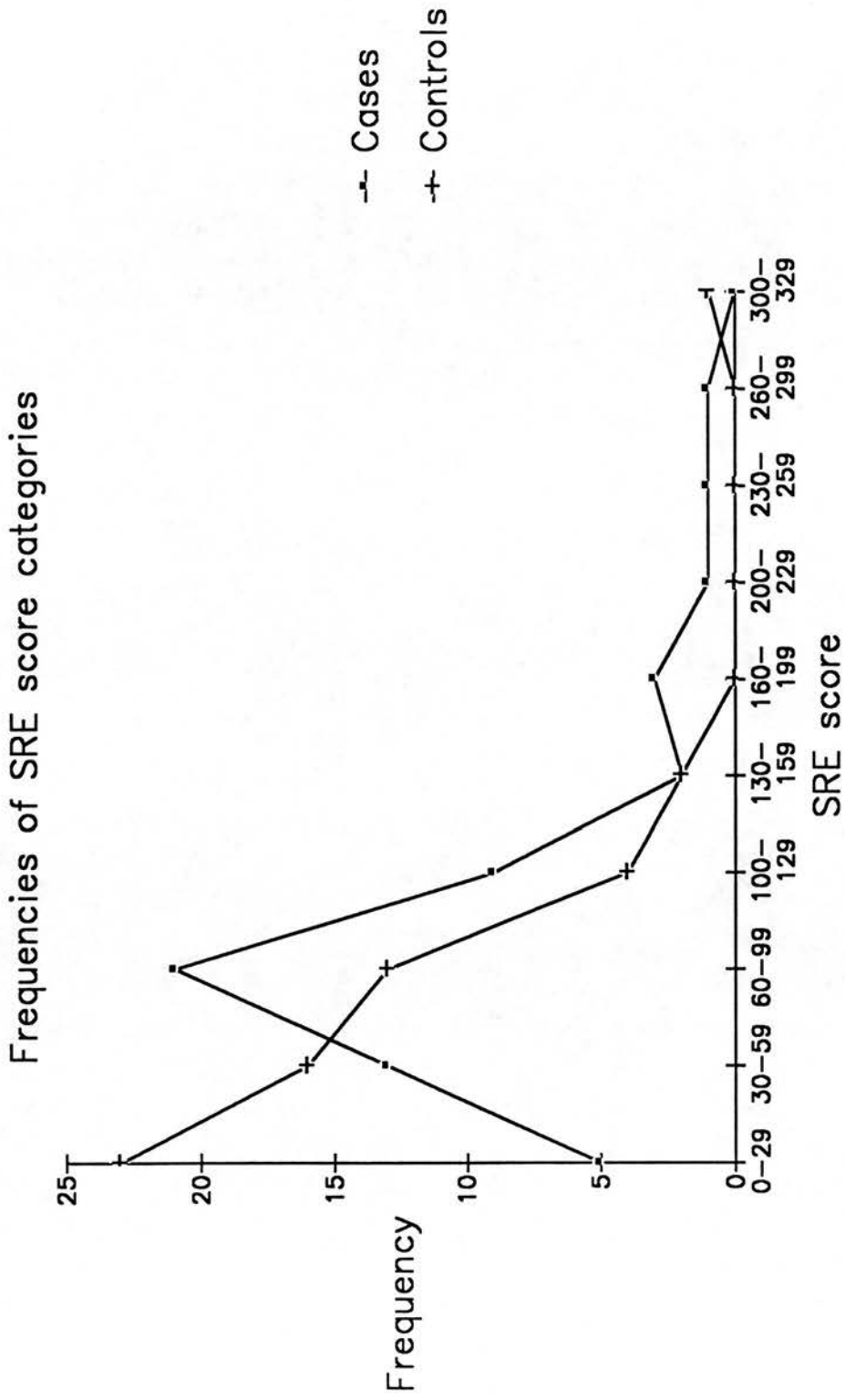


Table 39: History of gingivo stomatitis

	<u>Cases</u>	<u>Controls</u>
YES	0	2 (2.5%)

chi-squared 0.00 d.f. 1 p 1.00 95% C.I -0.11, 0.07

Table 40: History of cold sores / first noted

Those giving a clear history of cold sores

40 (51%) cases and 36 (49%) controls

chi-squared 0.25 d.f. 1 p. 0.62 95% C.I -0.11, 0.22

These were first noted:-

<u>When</u>	<u>Cases</u>	<u>Controls</u>
As a child	8 (19.5%)	17 (47.2%)
As a teenager	7 (17.1%)	6 (16.7%)
Over 20	10 (24.4%)	5 (13.9%)
Unable to say	16 (39%)	8 (22.2%)

cold sores first noted as a child versus not as a child

chi-squared 0.00 d.f. 1 p. 1.00 95% C.I -0.55, 0.30

Table 41: Summary of results - case control study

<u>VARIABLE</u>	<u>McNemar chi-squared (with continuity correction)</u>	<u>d.f</u>	<u>p.</u>	<u>95% C.I.</u>	
Positive family B.P. history	5.82	1	0.02	0.03	0.20
Family history diabetes	0.00	1	1.00	-0.11	0.14
History Menière's disease	0.50	1	0.48	-	-
History migraine	0.21	1	0.65	-0.15	0.07
History asthma	1.12	1	0.29	-0.13	0.02
History heart trouble	0.00	1	1.00	-0.04	0.07
History mouth ulcers	6.76	1	0.01	-0.34	0.06
History hypertension	2.12	1	0.15	-0.01	0.20
Alcohol consumption (previous 24 hours)	12.00	1	<0.001	-0.39	-0.11
Smoking habits	1.73	1	0.19	-0.04	0.28
Nailbiting habits	0.03	1	0.86	-0.12	0.17
Recent history of depressive illness	8.47	1	<0.01	0.07	0.28
An illness with a temperature -	6.86	1	0.01	0.05	0.29
URTI cough, cold or chest infection -	4.97	1	0.03	0.03	0.31
URTI sore throat	4.76	1	0.03	0.03	0.26
Exposure to draught	0.64	1	0.42	-0.04	0.15
Exposure to cold or chilling -	1.50	1	0.22	-0.01	0.11
Increased physical work or strain in previous 2 weeks -	2.08	1	0.15	-0.01	0.17
Exposure to bright sunlight in last 24 hours -	1.12	1	0.29	-0.02	0.12
Skin type	7.50	1	0.01	0.08	0.41
Emotional strain/stress over preceding month	9.76	1	<0.01	-0.44	-0.11
History gingivo stomatitis	0.00	1	1.00	-0.11	0.07
History of cold sores	0.25	1	0.62	-0.11	0.22
Cold sores first noted as a child v. not child -	0.00	1	1.00	-0.55	0.30

CHAPTER 11

Further Background to the Epidemiological Studies
and discussion of the results11.1 Introduction

The purpose of this chapter is to cite unequivocal evidence of relevance to the discussion, and at the same time highlight the complexity of linkages between proposed and supposedly simple aetiological factors such that the results are not interpreted in an oversimplistic or unthought out way.

Much of the research background and particularly that of relevance to the case-control (aetiological) study can be found in the first three chapters. This review then, examines a wide background under numerous headings which relate to either individual questions or themes in the questionnaires. These themes are firstly pure description of the clinical condition in British general practice and secondly aetiological themes. This second group includes genetic factors, physiological factors and HSV disease and its associations and also general factors of aetiological significance not readily fitting the above categories. The approach is however one based on particular clinical or epidemiological observations of value to the discussion. Later, expansion is made using humoral patterns as an epidemiological theme. The advantage of this is to show the possible interrelatedness rather than separateness of proposed aetiological factors. This discussion is under the headings of menstruation and pregnancy; Bell's palsy, diabetes and opioid sensitivity; and opioid sensitivity - further considerations. HSV reactivation and recrudescence are also reviewed at the end of this section - for although many aetiological agents are involved in these processes physiological "disorders"; "stress, menstruation or further humoral patterns are again discernible. This is highly relevant to the proposed aetiology of Bell's palsy because of the observed aetiological similarities".

The case control study examines for differences in "humoral patterns" between Bell's palsy cases and controls. The addition of an antibody study (for HSV) would give an indication of the proportion of cases (with negative serology) where humoral factors if present would have to be acting independently of an HSV associated aetiology.

Ideally any background review should be impartial and the author is aware of his own partial or selective bias which cannot be avoided in setting up such a study.

11.2 Clinical Incidence and Background

The incidence of 'intratemporal' facial palsy varies in Europe between 11.5 and 18.8 patients per 100,000 per year, although higher figures are reported from Egypt, Columbia and India (from the proceedings of the 3rd International Symposium on Facial Nerve Surgery, Ed. U. Fisch 1977). In America, Hauser (1971) calculated the incidence of Bell's palsy in Minnesota at 22.8 per 100,000 population per year. Verjaal in Holland (1955) estimated an incidence of 20 per 100,000 adults and 5 per 100,000 children. In a study by Fisch (1979) the percentage of cases of Bell's palsy occurring in children was 20.5% (365 patients total).

In Australia a survey (Seymour 1977) demonstrated that 57.6% of GP's see 1-3 cases of Bell's palsy a year, 37% see less than 1 case per year and 6% see more than 3 cases per year.

Hamberger collected a series of national incidence figures (cited by Fisch 1977):-

England	16.6	per 100,000 per year
Scotland	16	"
Norway North	18.8	"
Sweden South	11.5	"
Sweden Whole	16	"

In adult series the percentage of facial palsies classified as idiopathic is 63% (Cawthorne and Haynes 1956), 80% (Zulch 1970), and 66% (Tomita 1972). In children's series 60% were noted to be idiopathic by Manning and Adour 1972 but only 28% by Alberti and Biagioni 1977.

Adour in 1974 examined 419 patients in the San Francisco Bay area with Bell's palsy over a 3 year period. He found no evidence of periodicity or epidemicity considering the group as a whole or studying age-sex subgroups using Edwards (1961) method of statistical analysis. He concludes that a 'common cause' for Bell's palsy would have to be non-contagious, randomly distributed in a general population affect

persons of all age groups and not be temporally related to the seasons of the year (cases following a random Poisson distribution). However diseases involving a carrier or latent state and where subclinical illness is common, may confound easy explanations as for example did early attempts to understand polio epidemics. This may be argued to be the case in Bell's palsy which furthermore has a low incidence.

In 1978 Adour makes the unsupported assumption that epidemics do occur on the basis of his clinical impression but generally the disease appears not to be contagious. Brodie in a retrospective study of 104 cases found a lower incidence in the summer months May, June and July. El-Abiary and Leibowitz in an Egyptian study showed an increased incidence in August using age sub-groups.

Gomes (cited by Fisch 1977) has shown the incidence of Bell's palsy is greater at altitude (22 per 100,000 at 9,000ft) than sea level (15 per 100,000). He argues that a low atmospheric pressure 560mmHg, hypoxia and hypocarbia predispose to Bell's palsy, and that Bell's palsy was higher in the months in which there was more fluctuation in atmospheric pressure. Devreise (1982) however argues that atmospheric pressure influences the different pressure systems equally and accordingly does not disturb the pressure gradients.

11.2.1 Age-sex distribution

According to Adour (1978) the incidence of Bell's palsy increases with each decade of life but it is clear that these are not corrected incidence figures. The incidence reaches 30-35 per 100,000 per year after the age of 60. In this study the overall incidence of males to females was approximately equal, but in the second decade of life the condition was twice as common in females. Brodie (1979) found a ratio of 5:1, F:M in this decade, Hauser (1971) and El-Abiary (1971) also found an increased F:M ratio in this decade. Adour also noted that after the age of 40 Bell's palsy was 1.5x more common in males and suggested that this shows a relation to menarche and menopause.

11.2.2 Recurrence and side of palsy

El-Abriary (1971) noted recurrence was twice as common in females as males.

In Brodie's (1979) hospital based retrospective study 8.9% of the patients gave a history of previous facial palsy. Adour (1975) found a previous palsy in 9.4%. In two large retrospective series from Japan (Yanagihara N. et al. 1984) the incidence of recurrence was 2.2% (1,154 patients) and 2.0% (1,119 patients) for unilateral Bell's palsy. The incidence of bilateral disease was 0.7% and 1.2% respectively - for simultaneous palsies and 2.1% and 3.3% for alternating bilateral palsies.

Thus the majority of patients with Bell's palsy belong to the unilateral nonrecurrent type. Yanagihara found that male preponderance was apparent in the simultaneous bilateral type 20 patients (91%), and female preponderance in the unilateral recurrent type 31 patients (61%), particularly under 19 years of age. The interval between attacks is more than one year in the majority of cases.

11.2.3 Preceding exposure and associated symptoms

Adour (1978) records a preceding URTI in 20%, fever in only 2%, facial spasm in 22%, headache in 10%, fatigue in 3%, and facial numbness in 32% with undetermined symptoms in 36%. Peckert (1982) found that taste disturbance was commoner in non-diabetics, 83%, as opposed to those who had diabetes, 14%.

Adour (1974) found no evidence of an increased incidence in winter months rather than summer months. This does not really test the 'draught' hypothesis, as draughts cannot be quantified seasonally.

Pieterse (cited by U. Fisch 1977) gives the historical incidence of exposure to:-

draught	15%
colds and influenza	8%
(and preceding taste disorders in	35%)

However no control figures are given by either Adour or Pieterse in their studies.

11.2.4 Racial factors

Seymour (cited by U. Fisch 1977) reporting on the incidence of Bell's palsy found no difference between the general Australian population -

predominantly caucasian, and aborigines. Not only do aborigines differ genetically but they also exhibit a different pattern of primary H.S.V. infection. Unlike caucasians most primary infection occurs in early life (before 4 years) and the secondary peak in teenage years noted in Europeans is absent. It would be interesting to know if Bell's palsy occurred in a younger age group in aborigines than caucasians as this would give information as to whether timing of first exposure to HSV (primary infection) was important in developing Bell's palsy.

11.2.5 Genetic factors in Bell's palsy

A positive family history is one in which Bell's palsy occurs in a first degree relative i.e. parent, sibling, child, or second degree relative i.e. grandparent, grandchild, cousin, aunt, uncle, nephew or niece.

Alter in 1963 studied 105 patients with presumed Bell's palsy and found 30 of their relatives had a positive family history of facial paralysis which would fit with a diagnosis of Bell's palsy. In 105 controls he noted only 4 relatives had a history of paralysis. Alter concludes that Bell's palsy is a dominantly inherited disease with reduced penetrance.

De Santo and Shubert (1969) reported 10 cases of Bell's palsy in a single family spread over 83 years, but the highest reported family incidence of Bell's palsy was by Willebrand (1974) who noted 29 cases in three generations over 40 years. A 6% family history was noted by Willebrand out of 230 cases. This study also concluded that an autosomal dominant inheritance with incomplete penetration was the likely mode of inheritance.

Adour (1978) found that 8% of relatives had a positive family history of Bell's palsy and Brodie in a Scottish study found 13% of relatives had a positive family history. In neither study was a control rate given. A Mexican study (Alfonso-Vilatela 1979) gave the highest positive family history in world literature at 30.5% for first degree relatives and the control group figure was 3.6%. These authors propose multifactorial inheritance.

Autosomal dominant inheritance seems the most favoured. Presley (1978) a general practitioner observed 5 members of one family with Bell's palsy. Further support comes from Hilger 1949, Wilson and Bruce 1953, Danforth 1964 and Kakar et al 1966. Autosomal recessive inheritance was reported by Johnson and Stoesser 1937 and Danforth 1964.

11.2.6 Menstrual cycle

In Adour's 1978 study 123 women offered a menstrual history of 28 days. The rate of Bell's palsy was highest on the first menstrual days with a small secondary peak from day 11 to 17 (around the time of ovulation). 65% of cases occurred in the first half of the menstrual cycle with a sharp decline in incidence the week before the next menses. It appears that women who do not menstruate every 28 days were excluded from this study!

11.2.7 Pregnancy

Sir Charles Bell first suggested a possible association of facial paralysis with pregnancy in 1830. A number of authors have further studied this state for statistical correlation but because of few cases, Pope 1969, Korczyn 1971 and Robinson 1972 failed to demonstrate an association of Bell's palsy with pregnancy. Hilsinger in 1975 found the frequency of Bell's palsy in pregnant women was 45.1 per 100,000 births. Per year of exposure the increased risk of pregnant women was calculated as 3.3 x higher than for non-pregnant women in the same age groups. The incidence in the third trimester and puerperium was 118.2 per 100,000 per year of exposure, showing this to be the greatest 'at risk' period. Adour in 1978 apparently using the same cohort as Hilsinger states that Bell's palsy is 3x more likely to develop in the third trimester than in the first or second trimesters.

Table 42 : Observations in pregnancy and puerperium of Bell's palsy cases

	<u>Trimester</u>			<u>Puerperium</u>	<u>Total</u>
	1	2	3		
Hilsinger 1975	~~~~~			5	42
Adour 1978	1	8	28	7	44

From the above table it can be seen that the increased risk is actually

much greater, 10.3 (Hilsinger) and 6.5 (Adour) averaging the first two trimesters.

Although the numbers used in this study are small the finding of only 1 patient in the first trimester might be interpreted that early pregnancy has a protective effect on potential Bell's palsy sufferers!

11.3 Humoral Patterns

11.3.1 Menstruation and pregnancy

"The monthly activities of the ovaries which marks the advent of puberty in women has a notable effect upon the mind and body: wherefore it may become an important cause of mental and physical derangement"

- Henry Maudsley 1873. The diversity of such activity is well reviewed by Magos and Studd (1985).

Hilsinger in 1975 writes that "there was no apparent correlation between hormonal changes that characterize the phases of the menstrual cycle and the observed higher incidence of Bell's palsy during the first half of the cycle of the women in this series. These events also cast doubt on the possible aetiological relation of hormones to facial paralysis in pregnancy". However during that same year endogenous opioid peptides were discovered and much has since been done to define the complex physiology of these neuropeptides. Fachinetti¹ (1987) notes that β -endorphin levels have a rhythm throughout the normal menstrual cycle. The acrophase occurring around mid-cycle L.H. peak, and ovulation. In this study the plasma β -endorphin level (which seems to parallel CSF opioid activity - Fachinetti 1987²) varied very little. However in 11 patients with premenstrual syndrome a fall in β -endorphin activity occurred 8 days before menstruation with low levels occurring from 5 days before menstruation to the second or third day of menstruation with a peak of endorphin activity on the fourth day of menstruation ($p < 0.05$).

This pattern would appear to approximately mirror the observed incidence of Bell's palsy with the menstrual cycle, whereas oestrogen, progesterone, FSH and LH levels do not. As Bancroft (1985) states, it is difficult to be certain in view of the subjectivity involved how many women suffer from premenstrual syndrome - "but the possibility

that large numbers of women are adversely affected by premenstrual changes has to be taken seriously". This author quotes figures of between 29-97% from retrospective studies. Immature humoral cycles characterize the second decade of life, a group in which conceivably endorphin levels may fluctuate and predispose to Bell's palsy?

With respect to the menopause; β -endorphin levels are increased at the onset of subjective flushes and naloxone reduces the number of flushes as well as the number of L.H. pulses (Genazzani 1984, Lightman 1979, 1981) pointing to a role for opioid peptides in menopausal flushes. However some authors have disputed these findings (Tulandi 1985).

During human pregnancy plasma concentrations of ACTH and ACTH related peptides increase significantly (Csontos et al 1979, Carr et al 1981, Newnham et al 1983, Abou Samra et al 1984). β -endorphin rises from low plasma levels at 9-12 weeks to normal values at 13-16 weeks with further progressive and significant increases until term. At term the values are the highest recorded during pregnancy with maximum values occurring during delivery (Genazzani 1981). Fletcher et al (1980) found β -endorphin levels were low before labour but rose dramatically in second stage with the highest levels being recorded post partum (> 60 t mol/ml plasma of β E.L.I). The increased sense of well being and raised pain threshold of the puerperium suggests that β -endorphin levels remain high during this period.

Thus β -endorphin changes in pregnancy from low to high values also reflect the changing incidence of Bell's palsy throughout pregnancy and the puerperium. The correct interpretation of the significance of such an association however requires further information.

In pregnancy other peripheral neuropathies may occur such as brachial neuralgia and carpal tunnel syndrome. In the latter condition fluid retention is thought to cause compression and ischaemia of the median nerve under the flexor retinaculum. It has been speculated that Bell's palsy is caused by the involvement of the facial nerve in the oedema process, causing compression in the temporal bone. Mair points out that there is no association of Bell's palsy with the combined oral contraceptive pill, which also produces tissue oedema. Hilsinger (1975)

found no association of Bell's palsy with toxæmia of pregnancy, a condition also associated with tissue oedema. A further argument against oedema as a cause comes from the observation that the inferior alveolar nerve which also runs a long course through a bony canal is not affected during pregnancy.

Certain viral infections are commoner in pregnancy e.g. C.M.V. infection, also HSV infection is commoner in pregnancy (Naib 1973) and the lesions appear to be more severe. Gestational immunosuppression induced by high steroid levels is one theory as to why HSV may reactivate during pregnancy (Jewett 1975). HSV is also reactivated during menstruation and by rises in body temperature.

In conclusion it would appear that Bell's palsy is more likely to occur when β -endorphin levels are likely to be high and least common when the levels are likely to be low (premenstrually in some women and early pregnancy). It could be then that susceptibility to rapidly fluctuating levels of β -endorphin at menarche, menstrually and at ovulation, menopausally and later pregnancy and the puerperium, is the more important factor in such an hypothesis.

A viral reactivation hypothesis is also supported by the weak epidemiological evidence and it is the author's contention that either the viral or humoral hypotheses remain tenable upon reflection of these observations.

11.3.2 Diabetes, Bell's palsy and 'opioid sensitivity'

Adour in 1978 stated that Bell's palsy is 4.5 x more likely to develop in the diabetic than the non-diabetic person. The high incidence of diabetes in Bell's palsy patients noted by Korczyn (1971) has already been stated - with 66% of patients having abnormal G.T.T's or overt diabetes. Of 130 patients, 18 were known diabetics, another 8 had a fasting blood glucose above 130mg/100ml and 62 had abnormal G.T.T.'s. The author states that Bell's palsy may be the first manifestation of diabetes; and that in any patient presenting with this neurological deficit glucose tolerance should be checked. However it should be noted that the control frequency in the Israeli population is between 12-14%.

Adour in 1975 found an 11.4% incidence of diabetes in an American study. Pecket (1982) in another Israeli study found that out of 126 patients with Bell's palsy overt (chemical) diabetes mellitus was found in 39% of cases using Fajam and Conn's criteria (1959), and postulates that some cases of Bell's palsy may be a diabetic mononeuropathy. This figure might be further increased if Bell's palsy patients were followed up over a period of many years as many Bell's palsy patients suffer their condition at an age (mean age for this study 44 yrs) which pre-dates the likelihood of N.I.D.D developing (mean age 58 yrs, Burrows et al. 1987). Thus in this sense the strength of the association between the two conditions might be underestimated.

In a Dutch study Abraham-Inpijn 1982 could not find an association of diabetes with Bell's palsy using controls although the incidence was high in both; 56% in B.P. and 45% in controls using WHO criteria. Brodie's study revealed that only 2 of 104 cases were known diabetics, but was disadvantaged by being retrospective, and it is not clear if urine or blood was tested for glucose in all cases.

Factors which make studies difficult to interpret are geographical variations in the incidence of diabetes; the criteria by which diabetes is diagnosed; the sex and mean age of the screened group; the lack of controls; and the severity of the nerve lesion produced. Furthermore the more carefully any condition is looked for the more likely it is to be found.

It is interesting that other nerves affected by a mononeuropathy all traverse an anatomically enclosed space which makes them especially vulnerable to the effects of ischaemia (Richards 1951). Pecket argues because taste is spared more often in diabetes the lesion must be distal to the bifurcation of the facial nerve and chorda tympani. However this assumes that all fibre types myelinated and non-myelinated are affected equally by the disease process. Damage to the nerve is presumed to be due to a microangiopathy, but evidence for this is lacking histologically in Bell's palsy.

Diabetic mononeuropathy tends to occur in mild diabetes (N.I.D.D) of short duration, and independent of other types of diabetic neuropathy (Fraser 1979). Vascular manifestations of diabetes are thought to be

independent of the metabolic abnormality. Precisely how these vascular manifestations come about is unknown. Interestingly Pike in 1978 has defined a population genetically more susceptible to N.I.D.D. who flush with chlorpropamide and alcohol. He attributes this to an underlying sensitivity to opioid peptides. Although the mode of inheritance postulated has since been contested (autosomal dominant with impaired penetrance) the opioid hypothesis remains a tenable one.

To date several studies exist which confirm a strong genetic element in the transmission of susceptibility to Bell's palsy and considering the association of Bell's palsy with abnormal G.T.T's, it seems reasonable to suggest that those with "a genetically determined underlying sensitivity to opioids" are also a susceptible group for developing Bell's palsy. It is surprising that this hypothesis has not been advanced considering the epidemiological associations of "stress" with the onset of acute Bell's palsies.

11.3.3 Opioid sensitivity and further considerations

Individuals might be collectively grouped into those in whom production of endogenous opioid peptides has been increased for whatever reason, and those with receptor population distribution and characteristics determining a "sensitive" response.

Opioid sensitivity may be determined by receptor type with certain individuals more predisposed to respond. For example the kappa receptor is not significantly present in about 1/3rd of the general population as evidenced by only 1/3rd responding to pentazocine as an analgesic. Pentazocine is a kappa agonist with little demonstrable activity on μ or δ receptors. Little is known of the genetics of opioid receptor type distribution. N.I.D.D. has been postulated as an 'opioid sensitive' disease. Could the basis in both N.I.D.D. and Bell's palsy be connected with the kappa response? This would group certain individuals (approx. 1/3rd of the population) as opioid 'sensitive' who would be 'at risk' of developing either disease.

A variety of stimuli will increase the production of endogenous opioids (pituitary β -endorphin), cold stress, physical stresses, psychological or emotional stress, bright sunlight (POMC), menstruation, ovulation, late pregnancy and the puerperium. And some stimuli will

lower endogenous opioid production e.g. exogenous high dose steroid administration and early pregnancy. (These lists exclude endocrine diseases).

The effect of increasing age on opioid peptides is broadly to increase opioid receptor populations due to falling transmitter production. Early in life opioid receptors may be few. During periods of marked growth G.H. levels can be found to be raised and 'growing pains' may be due to low endorphin levels? These two hormones enjoy a reciprocal relationship with opioid pathways involved in control of G.H. release. During periods of rapid growth 0-7 and 12-20 the incidence of B.P. is low, except in the second group in young girls where maturation of menstrual cycle control may be a compounding factor. It is interesting to speculate why recurrent Bell's palsy should be most frequent in teenage girls, and this observation should surely lend weight to a humoral hypothesis.

Evidence of a circadian rhythm in the incidence of Bell's palsy would also lend support to a humoral hypothesis.

11.4 HSV Reactivation and Bell's Palsy

HSV reactivation is reviewed by Klein (1982). It must be admitted that little is known of the exact nature of HSV latency in neurones. Even less is known about the mechanisms of virus reactivation. Triggers to reactivation may occur at either the level of the ganglion or skin. If the ganglion is the site of reactivation then the virus must travel centrifugally to the periphery where it may then produce an infection of the skin or mucosa (recrudescent lesion). Longson (1970) writes that whatever the mechanism of the phenomenon of reactivation is, "reactivation of endogenous HSV to produce recurrent herpes is a common, almost physiological, even if unwelcomed 'fact of life' for almost half of mankind".

Factors associated with HSV reactivation in animal experiments include; section of the nerve (Walz et al 1974) intratracheal injection of pneumococci (Steven et al 1975) postganglionic neurectomy (Price and Schmitz 1978) cyclophosphamide or Xrays (Openshaw 1979) cyclophosphamide, prednisolone, antithymocyte serum or trauma to the ganglion (Hill et al

1981) dry ice on the lip (Openshaw 1979) cellophane type stripping/depilation, xylene, retinoic acid or DMSO (Harbour et al 1983). Of all these perhaps only intratracheal pneumococci is of direct relevance to Bell's palsy epidemiology where preceding URTI has been noted by Adour 1975. It is also puzzling that prednisolone may produce a reactivation (by immunosuppression?) yet at the same time be used to treat Bell's palsies.

It must be stated that there is still much to learn about the process of HSV neural reactivation and its likely frequency in human subjects. It is interesting to note that stimulation of the pain pathways or proto-pathic receptors produces reactivation.

11.4.1 Recurrent HSV and Bell's palsy

Recurrent HSV has been recognised for centuries:-

O'er ladies' lips, who straight in kisses dream.

Which oft the angry Mab with blisters plagues

Romeo and Juliet, Act I, Scene iv.

More recently Grout (1976) has described the epidemiology of cold sores in general practice. Wildy (1982) when describing recurrence states that "the factors leading up to it are so complex that except for immunological factors and mediators of inflammation - in particular the prostaglandins - little direct use can be made of the findings". He also considers "latency and reactivation in the ganglion represent a phenomenon quite distinct from recurrence of infection or recrudescence at the periphery". Thus factors associated with HSV recurrence and associated with Bell's palsy need cautious interpretation. Factors associated with recurrence include pyrexia (Warren 1940, Greenberg 1969) sunburn and UV light (Blyth 1976, Spruance 1985), trauma (Hill 1978) menstruation and pregnancy (Scott 1957) and stress (Schmidt 1985).

Of this list of factors all have been implicated in Bell's palsy aetiology. Of these stress and fatigue and UV light exposure have not been "quantified". In Schmidt's study the appearance of recurrent herpes labialis appeared to be related to "state not trait", that is to stressful life events and anxiety rather than personality factors.

However no studies to date have looked at recent stressful life events and Bell's palsy incidence. U.V. light exposure is difficult to quantify in a study of this type although the skin's response to U.V. light may be assessed (skin type). In both types of assessment controls are necessary.

Recent interest has focused on the role of surgical trauma and associated Bell's palsy. 6 cases being reported by Smith et al. (1990) on average 5 days after uncomplicated stapedectomy. The reasons for such delay in presentation though obscure could be conceivably related to the delay involved in ganglionic reactivation of HSV and in interferon/opioid production. Because of the comparative rarity of such procedures and the fact that recent head injury would have resulted in diagnostic exclusion, trauma was not examined as a possible aetiological agent in this study.

11.5 Comments on Results and Findings with Discussion of the Methods

The observers in the studies and the selection process

The patient, their families, friends and associates are the first observers of the illness and their sensitivities and responses will richly vary. The referral process begins with the patient him or herself and depends on the many factors which influence illness behaviour. In the case of Bell's palsy loss of power to the face has a 'frightening immediacy' to it, and older patients may think they are experiencing a stroke. It is highly likely therefore that patients with a noticeable weakness of the face will be seen by their practitioner. 70% of nerve fibres may degenerate before facial movements become noticeably weaker leading to the belief that sub-clinical Bell's palsy must be relatively common. Screening the population by electroneurography and seeing which patients develop a Bell's palsy is not a viable proposition however! This observation is unimportant from a descriptive standpoint but is highly relevant to the aetiological study.

There is an important difference in health status between the Bell's palsy cases and the relatively healthy controls which introduces a bias into the case-control study results. In my clinical experience patients generally possess a greater degree of sensitivity than healthy people in observing aspects of human behaviour as well as being involved in

self-rationalizing the phenomenon of illness. Furthermore ill people are more likely to consider themselves depressed than healthy people.

The General Practitioner as observer

By and large, Bell's palsy is a condition which general practitioners diagnose well. It is a clearly visible sudden weakness of the face, often in a young person. Only 2 false positives were noted by the author in 82 referrals. It should be noted that the GP's in the study were self-selecting, in terms of interest, with only 22.6% of all GP's contacted initially responding.

The author as observer

In this study a single observer was used to confirm the diagnosis of Bell's palsy and to interview cases and controls. This has both advantages and disadvantages. For all interviews (case and control), the disadvantages include observer bias (tends to be random), inconsistent application or lack of stringency in diagnostic criteria, and dangers of any systematic misclassification. The diagnosis of Bells palsy cases by the author correlates highly with the diagnosis achieved by other GP's. This consistency of observation only validates the general practitioners and the author if one accepts that adequately stringent criteria were applied by the author.

Bell's palsy and secondary care

Difficulties exist because of the referral system as to which specialist normally reviews Bell's palsy patients, but these include ENT surgeons, neurologists, general physicians, general surgeons, paediatricians and casualty consultants. Furthermore in Greater Manchester a patient with Bell's palsy might normally be seen in any of 20 district and teaching hospitals. The inpatient register would only identify those cases of Bell's palsy admitted to hospital which are very few compared to those seen in O.P.D.; and as a 1 in 10 sample cases may well be missed. Validation by means of hospital information was considered too problematical for a study of this size.

In some instances the practitioner decided to refer the patient to a hospital consultant but a large percentage (81%) were not so referred. It may be argued that this percentage is so large because

referral to the department acted as a "substitute hospital referral". The process of referral in this study differs from the usual 'vertical' referral to a hospital consultant, and is unusual inasmuch as it constitutes a more 'lateral' referral e.g. to a fellow general practitioner albeit in academic practice. Such a process is inherently selective, however severity, worrying clinical features, or patient demand should operate less strongly in this type of referral, given the nature of the study. On balance it is not unreasonable to suppose that this type of study generates more cases of less severe types of Bell's palsy and is more representative of Bell's palsy as seen in general practice; and may be reasonably claimed to be more typical of the natural history of the disease than is encountered in hospital.

11.6 Discussion of the Descriptive Epidemiological Study

This study is unique in being a large general practice based study of Bell's palsy in this country. Only $\frac{1}{5}$ th of cases were referred to hospital and so the study sets out features of the natural history of the condition as experienced in primary, rather than secondary care. Indeed, 37.5% of patients who had given a clear history of facial weakness, and whom the GP had diagnosed as Bell's palsy, had regained over 90% of facial function by three weeks. Thus, the case sample reflects, as one might expect, a high preponderance of less severely affected individuals, in which to study features of the condition. Although perhaps surprisingly this figure is not that different from Pietersen's (1982) study - 30% recovery at 1 month.

The study incidence is an approximation of the true incidence in as much as it can be determined. It does not take account of those cases not reported to the author for whatever reason, and no checking system could be reliably applied by the author, e.g. from hospital referral information. The incidence of 16.4 per 100,000 population per year is comparable with other European studies, however this figure is likely, by interpretation, to be a considerable underestimate.

Reporting throughout the study coincided more with the initial contact and an 8 month reminder letter, as can be inferred from the two peaks shown on the seasonal distribution histogram (fig. 10.1), with the March peak being two to three times higher than the previous

month. The FPCs were recruited over a limited period in June and July 1985 but reporting was until 1 August 1986 for all FPCs. This, comparing the recruiting period June/July 1985, 16 new cases were reported in those months, at a time when the study population was theoretically much less, compared to only three cases reported in June/July 1986. Thus, it appears that any seasonal trends are, in this study, unfortunately eclipsed by significant reporting differences as the study proceeded. What is of considerable interest is that the true incidence is likely to be of the order of two to three times higher than the quoted figure of 16.4 per 100,000 per year, it being impossible to accurately estimate the number of unreported cases.

It may be that Bell's palsy is commoner in the summer months, but a limitation of this study is that it has not been able to demonstrate this. Extending this study into consecutive years would still be difficult to interpret for the same reasons. Seasonal differences in most reported studies and indeed many inferences must be open to question if they are only reflecting the 19% of cases estimated to be referred to hospital by this study.

The fall-off in reporting might be taken to indicate that enthusiasm for the study rather than clinical features was a more common reason for referral into the study.

Table 6 shows that GPs in different FPC areas responded differently to reporting throughout the study. Rochdale, for example, contained a higher proportion of consistent responders, as evidenced by their reply to the reminder letter.

11.6.1 Geographical distribution and contact enquiry

From the map (A3 pullout) it can be seen that the distribution of cases is fairly uniform, with no particular FPC area showing a preponderance. There is no excess in the number of reported cases when comparing North and South Manchester as was thought half way through the study, and no strong evidence of clustering. The Wythenshawe area in South Manchester shows seven cases in near proximity but careful enquiry about social contacts, school and work environments revealed no common denominator to suggest transmission of infection. Thus the geographical distribution of cases in the study provides no evidence to suggest an infective cause

of Bell's palsy. Cases appearing to occur in a 'random fashion'.

11.6.2 Age distribution

The age distribution of cases of Bell's palsy shows that the 50-60 age group reveals the highest incidence of Bell's palsy. Paralysis is also noted to be common in 20-40 year olds. The bimodal distribution shown in some studies is not here demonstrated.

When correction is made for the age characteristics of the Greater Manchester population, it would appear that individuals have a decreased risk of acquiring Bell's palsy up to the age of 25 and an increased risk after this age (up to 75 years of age). Thus any apparent peaks of increased incidence in younger children, as reported in some studies in 6-12 year olds, may represent a greater willingness amongst GPs to refer such young children. The age distribution does not suggest a primary infection as the cause of Bell's palsy or degenerative diseases.

11.6.3 Social group distribution

The majority of cases of Bell's palsy occurred in Social Group 4 (= 3 Manual) reflecting the social distribution of the Greater Manchester population. No discernible trend can be identified from the study, again making a primary infection with HSV a less likely cause of Bell's palsy.

11.6.4 Ethnic origin distribution

Only 8 cases occurred in non-caucasians which is commensurate with the preponderance of races distributed in the community.

11.6.5 Sex incidence, side and recurrence

A male to female ratio of 1 : 1.3 shows a slight female preponderance, which a larger general practice study might confirm. The side of the paralysis was approximately equal, with 39 cases being right sided and 41 cases being left sided in keeping with the literature. No bilateral palsies were noted in this study.

Recurrent paralysis was noted in three cases or 3.75%, confirming the idea that Bell's palsy is, indeed, for most people a "once in a lifetime event".

11.6.6 Time of day paralysis noted

Bell's palsy, being a fairly notable event, is often clearly remembered by individuals with respect to the time of day of its occurrence. The majority of patients (70%) awake with the paralysis or develop it soon after, whereas only 30% of patients develop the paralysis in the last 12 hours of the day. It would thus appear that a true diurnal variation exists for Bell's palsy. This in turn suggests that an individual's physiological state is important for the timing of the onset of Bell's palsy, and perhaps even for its initiation.

11.6.7 Menstrual cycle, pregnancy and Bell's palsy

In this study, 11 women gave a clear menstrual history as defined by their being able to remember accurately or having recorded it, and were able to remember the time of onset of the paralysis. Of these, eight cases occurred during the first half of the menstrual cycle and three in the second half. This study records insufficient numbers to make a meaningful statement, but is in keeping with the findings of Adour's and Hilsinger's studies, which show a similar pattern.

Five women were pregnant or had just had a baby. The distribution was zero in the first trimester, one in the second, two in the third and two in the puerperium, again in keeping with the findings of the previous studies, and also that of McGregor (1987). This supports the belief that a humoral effect related to menstruation and pregnancy may be involved in the aetiology of Bell's palsy. Furthermore, 12 cases occurred in women in the peri-menopausal age group (46-56), (compared to 6 cases in men of the same age group), a group in which the endorphin levels might be expected to fluctuate markedly, supporting the general view of an opioid aetiology. The findings of this study contrast with Adour's study in which he found a male preponderance in this age group.

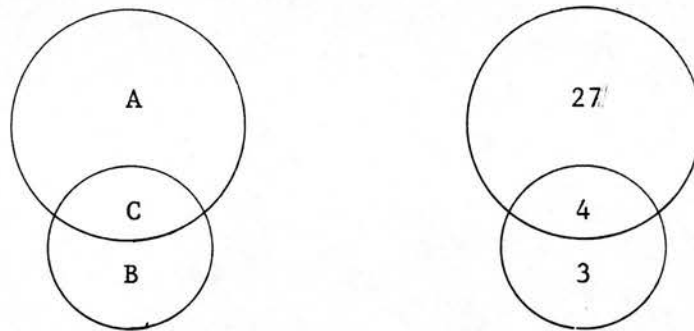
11.6.8 Indication of speed of onset

It is a common clinical experience that Bell's palsy is of a dramatically acute onset; that is, a sudden weakness which develops over several hours. It was asked how long it was between last noticing normal facial movements and 'noticeable' weakness, thus introducing considerable leeway for variations in memory and interpretation. However, it was felt to be a rough guide to the suddenness of the onset of the palsy. The

Fig. 11.11

Venn diagram of symptom reporting; altered or diminished sensation to the face?

Cases only



Key:

- A - History of left facial numbness = 1 or
history of right facial numbness = 1
- B - History of burning or flushed sensation to face = 1
- C - History of left facial numbness = 1 or
history of right facial numbness = 1 and
history of burning or flushed sensation to face = 1

majority of patients noticed it had developed in between six and twelve hours, and this often corresponded to going to bed with nothing amiss to awaking with the palsy, or noting it soon afterwards. The very suddenness of the onset suggests a vascular mechanism, although acute demyelination from other causes is a reasonable alternative explanation.

11.6.9 Associated symptoms

Interpretation of the significance of reported symptoms can be a variably difficult task. Numbness of the face, for example, being a particularly difficult symptom to interpret. It might be supposed that an inability to move the face would be described as numbness by some respondents, and for this reason an additional explanation was always given during the interview, including the description of "numbness like that experienced after a dental injection". Burning of the face was also included as a separate question suggesting paraesthesia, but might also be interpreted as facial flushing (see fig. 11.11). Overall, the tabulation of the associated symptoms represents a description of these symptoms as experienced in general practice. Perhaps surprisingly, depending on interpretation, there is still evidence of polyneuropathy, with the 5th nerve being involved in 38.8% of cases in this study, which is comparable with Adour's hospital-based figure. This is of some interest, and indeed suggests that referral tends not to be on this basis.

11.6.10 Taste alteration

This important symptom is discussed separately because of its relevance to the aetiology of Bell's palsy and the suspected level of nerve damage. Of the 80 cases of Bell's palsy in this study, 30 or 37.5% gave a history of taste disturbance and of these, 66% noted the disturbance before facial weakness and 14% noticed it after the onset of facial weakness, with 20% noting it approximately coincidental with the weakness. This suggests that the smaller, non-myelinated axons are more sensitive and damaged earlier than the larger motor neurones, or possibly that this disturbance is, in fact, initially a physiological hyperpolarization of neurones or nerve block (taste fibres being first affected by the virus, by the ascending chorda tympani route?). Although 60% of patients appears a large proportion of cases to give no history of taste disturbance if the disease is primarily geniculate in origin, it must be considered that a unilateral loss of taste may not be notable.

to an individual unless it is "altered" in some way, e.g. becomes metallic; or is tested for. Interferon-induced neuropathies may also produce taste and smell disorders; although these are extremely uncommon they are the pathways most frequently affected.

11.6.11 Examination findings

More substantive evidence of polyneuropathy in particular of 5th nerve involvement was found on examination in 12 or 15% of cases (diminution of pin prick sensation). No abnormality was noted of the palatal reflex in any cases (9th nerve involvement).

Glycosuria was noted in 8 out of 43 patients or 18.6% who provided urine specimens. However the sensitivity and specificity of this test does not allow meaningful conclusions to be drawn. Fasting blood glucose would have been better but was not feasible in this study.

11.7 The Antibody Study

To determine the exposure to HSV in Bell's palsy cases, 46 patients who agreed, had blood samples taken after the onset of the facial weakness (usually by 3 weeks). Twelve, or approximately a quarter of cases had no discernible complement fixing antibodies to HSV. Only three patients had titres of 1 in 80 or above. Of 12 paired antisera no significant rises were noted to HSV CF Ab, but one patient had a significant elevation of Cf Ab's to VZV (out of 9 paired antisera). The results of this small study indicate that HSV is unlikely to be a ubiquitous cause of Bell's palsy with no discernible antibodies in a quarter of patients and in contrast to Adour's study, no patients had high titres to HSV.

11.8 Facial Nerve Damage and Recovery

Facial nerve function was assessed at the initial examination and at a minimum interval of 6 months after the paralysis by means of a letter (Appendix 2c) with 18 of the non-respondents having to be contacted by telephone. An estimation of complete recovery occurred in 60 or 82% of patients with 13 or 18% making an incomplete recovery. Again this figure is comparable with Pietersen's 1982 study if his grades 0 and I are combined - 84% recovery. Problems with lacrimation occurred in 8 patients, 7 had loss of power, and 5 had hyperacusis.

Table 43: Assessment for factors associated with prolonged paralysis
(otalgia and age)

MANN-WHITNEY U TESTS

Interquartile							
	n	Median Range		p	95%CI		
<u>Paralysis Duration</u>							
Otalgia = Yes	15	8.00	3.00	12.00	0.10	0.00	6.00
Otalgia = No	26	5.50	3.00	6.00			

Paralysis Duration

Age	50	26	5.50	3.00	8.00	0.31	-5.00	1.00
Age \geq	50	15	6.00	3.00 12.00				

NON-PARAMETRIC CORRELATION

Spearman rank correlation for duration of paralysis versus age
 = 0.18, n = 41, p = 0.26.

11.9 Analysis for Prognostic Features

Several workers have noted unfavourable prognostic associations such as age (Taverner 1971) and taste disturbance (Adour 1974, Pecket 1982) and intrauricular pain (Taverner 1959, McGovern 1966) with outcomes in Bell's palsy.

To make a realistic assessment of outcome cases need to be assessed in terms of severity in relation to time. This fragmentation reduced the power of the epidemiological study. A further confounding variable of the utmost importance is the type of treatment and its commencement in relationship to the onset of the paralysis (Taverner 1971). Although tabulated in this study there was insufficient power to consider the effects of this variable.

Again, although it was not the primary aim of the epidemiological study to look for outcomes, information was processed using Mann-Whitney U tests for all likely determinants of poor outcome. Duration of paralysis with respect to age and pain in the ear are presented in Table 40. It can be seen that this study does not have the power to reveal a statistically significant association.

11.10 Discussion of the Case Control Study

11.10.1 Genetic factors

The number of cases of Bell's palsy with a positive family history was 13.8% comparable with Brodie's retrospective study (13%). Of these relatives 69% were first degree and 31% second degree. The majority of individuals had only 1 affected relative although several had more than one. The frequency of attacks did not approach that of Presley's study from general practice (6 attacks in 5 relatives). The control history was 1.3% for Bell's palsy. The McNemar chi square was 5.82 and a p value of 0.02 revealing a significant association of Bell's palsy with a family history of Bell's palsy. It could be argued that patients with Bell's palsy are more likely to have thought about possible affected relatives or had instituted inquiries whereas controls may have revealed less perception of family history and or a greater reluctance not to "label" dubious historical events as "Bell's palsy". Nonetheless controls were asked to think carefully about possible affected relatives and it is argued that the study does provide the much needed control information needed for interpretation of the findings in Bell's palsy cases.

In conclusion genetic factors are likely to play a significant role in predisposing to Bell's palsy.

11.10.2 Family history and diabetes

Non-insulin dependent diabetes appeared to occur with the same frequency in Bell's palsy and control group relatives. It is known that like Bell's palsy genetic factors are involved in the aetiology of N.I.D.D. With an incidence of N.I.D.D. at 1-2% in the general population a family history of between 10-20% though high would not appear to be significant. However the finding that 3 cases and 0 controls had personally been diagnosed as N.I.D. Diabetics and the finding of significant glycosuria in 8 out of 43 patients does suggest an association with diabetes. It is possible that the control figure is abnormally high in this study and it is apparent that the power of the study is not such as to demonstrate a genetic association between the two conditions if it exists. Those patients who also had a family history of Bell's palsy were too few to examine for differences in history of diabetic relatives.

Thus in terms of an association with non-insulin dependent diabetes, this study remains inconclusive but does tend to weakly support those studies showing an association with diabetes.

11.10.3 Drug history

A limited enquiry was made into the drug taking history to see if any associations existed between medication and Bell's palsy. In particular chlorpropamide, which might induce flushing was noted not to be the method of control for the 3 N.I.D.D.'s. Analgesics such as opioid agonists were not regularly taken by cases or controls. Pentazocine which might be expected to be only effective in individuals with Kappa receptors was not taken by either cases or controls.

11.10.4 Past medical history

This enquiry was made to explore possible associations between various neurological, herpetic and common diseases with Bell's palsy. It further allowed assessment of reporting differences between cases and controls by comparison with known frequencies for the incidence of these conditions. The only significant association appeared to be a negative correlation of mouth ulcers with Bell's palsy $p=0.01$ (13% of cases and 32% of

controls) which is interesting on 2 accounts. Firstly HSV has been speculated although somewhat dubious cause of mouth ulcers and secondly they occur more frequently in stressed individuals. (The Bell's palsy cases were the more stressed group in this study). The lifetime prevalence of recurrent apthous ulcerations in this country is 20.1% (Sircus 1957). It is likely therefore that the Bell's palsy group have a low incidence of apthous ulceration when considering other studies (Embil 1975) give prevalence figures of 66% for recurrent apthous ulceration. The lifetime prevalence figures do depend on long term memory but the cumulative effect of age should be eliminated in this study by the match pair analysis.

This negative correlation of Bell's palsy with mouth ulcers, far from disproving an association with HSV if it is a cause of mouth ulcers, could in fact be an observation of a complex relationship of HSV with its host.

A further point of interest is that a history of hypertension was not significantly different between the group, contrary to some findings in Bell's palsy studies (Abraham-Inpijn 1982, 1987).

11.10.5 Habits

Nailbiting appeared no different between the two groups in the subgroup of recurrent palsies, a condition in which conceivably herpetic transmission from hand to mouth might be relevant, numbers were too small to derive any conclusions. Smoking as defined by taking 1 cigarette or more per day appeared to be no different between the groups.

11.10.6 Alcohol

The taking of alcohol in the previous 24 hours for control, and 24 hours prior to the paralysis for cases appears to be significantly different between the two groups $p < 0.001$. This effect could be explained by the fact that cases were recalling events on average 3 weeks earlier and may have forgotten previous alcohol consumption. If Bell's palsy patients had a generally low consumption of alcohol this comparison might still be valid. A better enquiry would have been into normal drinking habits and approximate number of units consumed per week.

11.10.7 Draughts and chilling

The classical explanation of sitting in a draught showed no statistically significant difference in exposure between cases and controls. Again differences in memory over different time periods between cases and controls have to be considered. Nonetheless there would not appear to be a significant association. Severe cold or chilling, more likely to be remembered, did not reach a significant level of association.

11.10.8 Preceding physical strain

Increased physical strain or work appeared to be no different between the groups in terms of preceding exposure.

11.10.9 Preceding infection

It is known that Bell's palsy often follows on after an upper respiratory infection. This study showed significant differences between cases and controls in reporting preceding upper respiratory infection. Given the seasonal variation of many viral illnesses and the lag in interviewing controls it is possible that seasonal effects may be causing differences between the groups. However considering the study year the incidence of respiratory infection is not only higher in Bell's palsy patients than controls but also higher than predicted taking the frequency of coryza in the population as 3 or 4 attacks per year. This further strengthens the case for an association between the two.

However perhaps the most interesting conclusion and the most statistically significant is that "any illness in which the patient perceived they had a temperature" was more likely to have occurred in the two weeks prior to the onset of facial weakness than in the preceding 2 weeks for controls. A reasonable hypothesis from this information would be that "herpes febrilis" is being reactivated by a preceding illness. An alternative explanation is that numerous viruses produce Bell's palsy by producing a pyrexia.

11.10.10 Skin-type and Bell's palsy

Although preceding exposure to bright sunlight appeared to be no different between cases and controls the type of skin possessed by an individual in terms of "sensitivity to sunlight" was felt to be an important subsidiary question (vide infra).

Four grades of "skin sensitivity" to sunlight were designated in the study; as predominantly burning; tending to burn more than tan; tending to tan more than burn; and predominantly tanning when exposed to the sun. The numbers in each of these self assessed groups was fairly even for the controls, but showing a higher proportion of cases in the "predominantly burning" group. For the purposes of analysis the first two groups and the second two groups were combined and a McNemar test performed. The chi squared test was 7.5 and $p < 0.01$ shows a significant difference between the groups. Thus it would appear that fair skinned people are at greater risk of developing a Bell's palsy. This is not however supported from incidence studies comparing Norway with Columbia for example. Racial and genetic determinants may explain these differences. In this study all non-caucasian races were excluded from analysis.

The explanation as to why sunlight is associated with cold sores is likely to be due to prostaglandin levels in the skin being elevated facilitating the development of recrudescant lesions rather than reactivations (Hill and Blythe, 1976, skin trigger theory). A further problem considering skin triggers is the fact that the facial nerves somatic sensory distribution is confined to the ear canal, an area unlikely to be exposed to sunlight! The systemic response to sunlight may however well be different between fair and tanned individuals - with differing P.O.M.C. and endorphin levels and these constitute physiological variables of possible significance in terms of ganglionic reactivation.

11.10.11 Stress, depression and Bell's palsy

Subjective assessment of emotional strain was assessed in the month preceding the paralysis for cases and preceding month for controls. The patient was first encouraged to speak openly, and then asked if they felt this emotional strain was less than normal, about the normal amount, more than normal or much more than normal. For the purposes of analysis the first two and second two groups were combined. A McNemar chi squared test with continuity correction gave a value of 9.76 and a p value of <0.01 showing a significant association of a subjective assessment of increased emotional strain in the preceding month with Bell's palsy.

Table 44

MANN-WHITNEY U TESTS for associations between SRE scores and subjective assessment of normal or greater than normal emotional strain.

		Interquartile		p	95% CI		
	n	Median	Range				
<u>SRE Rating</u>							
Subjective stress							
category = Normal	65	46.00	25.00, 76.00	<0.001	-45.90, -17.00		
" = > Normal	50	75.00	49.50, 109.00				

Table 45

CHI-SQUARE TESTS

Recent history of depression and subjective stress categories

		Recent history of depression	
		YES	NO
Subjective stress category	Normal	3	100
Subjective stress category	> Normal	16	38
		19	138

A further assessment of stress in the preceding 6 months was made by using a self administered SRE checklist with a brief explanation to cases and controls. The results can be seen in Fig. 10.10 showing that higher scores between 130-260 were much more frequent in Bell's palsy cases than their age and sex matched controls. These results tend to confirm the findings of subjective emotional strain assessment. As a means of validating the data on stress from the subjective and SRE assessment, one would expect to find an association between a stress category of greater than normal versus normal in the subjective emotional strain response and the SRE score. This association was assessed by using the Mann-Whitney U Test (see table 45 opposite).

Thus, the difference in the median SRE ratings of subjective stress category normal cases versus > normal cases is $46.00 - 75.00 = -29.00$. Thus it is estimated that the SRE rating will be 29% lower in normal cases than in > normal cases. The 95% CI for the difference ranges from -45.90% to -17.00%.

Before claiming that differences in the groups are due to differences in subjective feelings of stress or recent life events, confounding variables should be considered. One such variable is a recent history of depression, which when assessed by the author for an intermediate period of 3 months appeared to be significantly different between the two groups $p < 0.01$. It is known that people with depression are likely to have experienced a recent life event, and this is implied in the definition "reactive depression".

When a statistical test (chi-square) is made for the association between subjective assessment of emotional strain and history of recent depression as interpreted by the author, it can be seen from the results that there is a very significant association $p < 0.001$. This further confirms the validity of the study information and also reveals the difficulties in too simplistic an approach when trying to interpret information concerning the interrelated variables of subjective assessment of stress, recent life events and recent depression. From table 46 opposite it can be determined that a recent history of depression and a subjective assessment of greater than normal emotional strain are significantly associated. The $\chi^2 = 21.3$ $df = 1$ $p < 0.001$ 95% CI = 0.747, -0.37. It is estimated that there will be 56.7% fewer cases

with a normal subjective stress assessment in those who give a history of recent depression than those who do not.

In conclusion subjective assessments whether made by the patient or the author show a significant association of increased emotional strain and depression before the occurrence of a Bell's palsy when compared with age and sex matched controls. Furthermore the highest SRE scores occurred much more frequently in the cases than the controls. It is argued that this evidence taken as a whole, even allowing for differences in health status between the groups strongly supports the notion that depression, emotional strain and recent life events are significantly associated with Bell's palsies.

11.10.12 History of HSV exposure

McCormick when postulating on HSV and Bell's palsy wrote that an increased incidence of cold sores in patients with Bell's palsy would tend to confirm his theory. The findings of this study are all essentially negative. There was no correlation between history of cold sores in the Bell's palsy and control groups. Both suffered them with comparable frequency. However it is quite erroneous to presume recrudescient lesions (cold sores) are equivalent to reactivation of HSV. Although a positive association here would have been helpful in strengthening the association of HSV "disease" and Bell's palsy, lack of correlation has very little to offer against an HSV "reactivation" theory, especially if one accepts Hill and Blythe's animal model in which neural reactivations are believed to be frequent subclinical occurrences. Furthermore a study group of approximately twice the size would be needed to have sufficient power to show a 10% difference in cold sore history between the groups (Machin and Campbell 1987).

Similarly no correlation could be found between age of first noticing cold sores between the groups suggesting the time of primary infection with HSV has no significance in the aetiology of Bell's palsy, although memory factors and study size make these conclusions rather weak. History of primary infection with HSV was remembered by only a few of the study participants.

CHAPTER 12

Concluding Chapter

12.1 Summary

The purpose of this chapter is to discuss and summarize the findings of the temporal bone and epidemiological studies, to consider further the implications, and the direction of future research.

Firstly, it would appear that the two studies are somewhat at variance. For example, the temporal bone study suggests herpes simplex virus is ubiquitously resident in the geniculate ganglion of the population. However, the epidemiological study could not demonstrate herpes simplex virus antibodies in 25% of cases. In the epidemiological study, the history of cold sores between the two groups appeared to be no different.

The findings of the temporal bone study are likely to be very significant if they are repeatable. Not only in terms of explaining an aetiological mechanism in Bell's palsy, but in their own right, and with respect to a route of entry of herpes simplex virus to the Central Nervous System in herpes encephalitis. The implications of this study are firstly that it is quite possible for herpes simplex virus to be a cause of Bell's palsy, since it is usually resident in the geniculate ganglion of the general population; in this much the hypothesis resisted falsification. However, the converse argument also becomes more forceful because of the observed frequency, namely that the observation of that which is frequent cannot alone explain that which evidence suggests occurs infrequently. Thus, these arguments present limitations to the inferences that can be drawn from such a study and indeed are inherent in its design. It has, however, provided further information to consider which, if repeatable, should be taken into account by other researchers when considering the aetiology of Bell's palsy. Although herpes simplex virus has not thus far been grown by co-cultivation from geniculate ganglia, from fresh specimens or cadavers, the findings of the virus in biopsy material would have to be interpreted with caution.

In summary, the results of the virological temporal bone study here presented are "permissive" of the outlined hypothesis. The hypothesis requires further evidence as to how and which factors operate selectively to limit

the frequency of Bell's palsy to that observed. In effect, if herpes simplex virus is involved in Bell's palsy, it is part of a multi-factorial process.

The epidemiological study, on its own, is an outline of a condition not reported to this extent in general practice in this country. As such, it is hoped it may be used as a reference description of the clinical condition of Bell's palsy. Reporting differences by GPs in this particular study suggests that the incidence of Bell's palsy is, in fact, higher than that previously reported in most of the world literature. Taken as a whole, and upon reflection of the findings of the descriptive study, the forcefulness of the patterns suggesting the importance of humoral and physiological factors in the mechanism in Bell's palsy are quite striking.

Those features identified from the epidemiological studies most likely to be associated with Bell's palsy are the 25-75 age group, particularly advancing age, being fair skinned as defined by burning rather than tanning in the sun, having a positive family history of Bell's palsy, being subjectively under more than the normal amount of emotional strain, having a higher SRE score and being depressed, having had an illness with a temperature in the previous two weeks or upper respiratory infection, being in the later stages of pregnancy, peri menopausal or in the first half of the menstrual cycle, during the first 12 hours of the day and not having a history of mouth ulcers.

A history of hypertension was no different between the groups nor is the history of cold sores. The findings of the antibody study contrasted with those of Adour in not finding "high but stationary antibody levels to HSV in the majority of individuals", but rather no significantly high levels, and in 25% no discernable C.F. antibody to HSV at all!

The association of Bell's palsy with diabetes remains unresolved by this study with 3 cases of N.I.D.D. identified out of 80 cases but no controls. It does however seem likely from other work involving G.T.T.'s that there is an association which this study failed to demonstrate.

12.2 The Hypothesis in the Light of the Evidence

The hypothesis discussed is an ambitious one and the evidence from these studies by comparison modest. One can take the view that the mechanism(s) of Bell's palsy will always be a riddle, or that much depends on future discovery, or that to look for a common mechanism is a categorical mistake. All these views however can be criticised on a basis of failing to assess current if somewhat diverse evidence and the first and last views as alien to the empirical approach on which science is based.

Taking the results of the temporal bone study first HSV would appear to reside in the geniculate ganglia of the general population to such an extent that it cannot account for a condition of such low incidence. Clearly the process of reactivation is central to the hypothesis and it is by no means certain or inevitable that persistence in afferent ganglia of the virus implies it will reactivate. In vivo tissue culture studies suggest neural reactivation is a one-off event (Wildy 1982), whereas work by Hill and Blyth (1976) in mice suggests neural reactivations are frequent but decreasing with time or application of the stimulus. If one inclines to the latter view, but bearing in mind that mice are not the natural host of HSV, then the results of the temporal bone study emphasize the need to consider a multifactorial aetiology. If one inclines to the former view it is less important to consider the aetiology in terms of a multifactorial process.

Secondly considering the results of the epidemiological studies there appears much to support a multifactorial aetiology in Bell's palsy. Firstly there is the disappointing evidence for protagonists of HSV as a sole cause from the antibody study, where it is clear that some individuals do not appear to have antibodies to HSV at all. The antibody study itself might be criticized in terms of few paired antisera being taken, its small size, and the fact that some bloods would have been taken before it might presumably be expected antibodies to develop. Nonetheless it appears HSV cannot be a universal cause, and this is supported by other negative antibody studies.

The case control studies suggest the importance of genetic factors in the aetiology of Bell's palsy. If one also considers the work showing a strong association of N.I.D.D. with Bell's palsy perhaps in up to 50% of cases then it is tempting to speculate a common genetic link between

the two. This link may be in terms of an underlying sensitivity to opioid peptides. This is particularly pertinent when one considers that chlorpropamide alcohol flushing must involve (by intelligent speculation) the branches of the external carotid supplying the supragenulate part of the facial nerve.

Further evidence for a complex aetiology comes from the variety of "physiological stressors" which are associated with Bell's palsy. When considering the response of biological systems to stress it is perhaps too easy to fall into the trap of unification by labelling what is in fact a diverse and complex system i.e. that of the opioid peptides; and by unnecessary speculation in areas where little evidence exists. Such is not the purpose of epidemiological research but rather by observation and reflection of curious features of Bell's palsy to discern patterns and decide what is or may be common features unique to Bell's palsy but not controls. "Stress" is common and patterns of stressors likely to repeat themselves. Bell's palsy by and large is not common and does not repeat itself. Therefore if "stress" is acting in the mechanism its actions are triggering or magnifying some other process which occurs infrequently or is infrequently noticed, or the resultant disease process renders unlikely to happen again.

The patterns discerned in the epidemiological study are indeed compatible with what little is known about the neural reactivation process of HSV and this process may itself be a means of amplifying the stress response at least locally to the ganglia (or part of the CNS) in which it occurs. Furthermore though this process may be frequent the extent to which a significant or marked peptide/vascular response is produced is likely to be much less frequent.

The hypothesis outlined is further dependent on an increased production of interferon and opioid peptides from ganglion cells which of themselves, the author suggests, produce damage by sustained vasodilation. It can reasonably be speculated that this process will vary biologically in terms of both output, the half life of the peptide, their removal rate and the vascular sensitivity or responsiveness. This system or series of systems might go some way to explaining how stress operates selectively with only sensitive individuals or those with a high/sustained interferon/opioid output producing sufficient vasodilation to produce clinically noticeable events.

Anatomical factors may also be of critical importance in determining the frequency of serious nerve damage. Of particular relevance is the diameter of the entrance to the Fallopian canal.

Interferon levels but not opioid peptide levels have been studied in Bell's palsy. Aviel has demonstrated that interferon levels are often high in Bell's palsy. The finding in this study that an illness with a temperature often preceded Bell's palsy again might suggest a role for interferon, which together with prostaglandins is incriminated in producing pyrexia.

In summary the extended hypothesis appears to withstand the evidence with the proviso that other stimuli of the interferon opioid system e.g. other viruses might reasonably act as triggers for the interferon/opioid/vascular mechanism. The proof of the hypothesis however lies with further research.

12.3 Suggested Further Research

Very little is known of the genetics of opioid receptor distribution in populations. This would be most interesting to study and in particular whether there are common links with for example the Kappa receptor, Bell's palsy and N.I.D.D. Chlorpropamide alcohol flushing could be performed in patients with Bell's palsy and if the incidence observed, were high, similar to that found in N.I.D.D.'s this would tend to confirm the hypothesis.

Larger general practice studies might further be performed over longer periods of time to look for trends or seasonal variation. Other clinical studies might include double-blind placebo controlled trials of Naloxone in Bell's palsy with improved outcomes in the treatment group tending to confirm the hypothesis. Blood or CSF interferon or endorphin levels might further be studied in Bell's palsy. Local enkephalin levels in the CSF in the proximity of the nerve would prove problematical in obtaining and in interpreting where delay was involved.

Further work in understanding interferon neuropathy and whether this might be a vascular effect would be most interesting.

Animal experiments perhaps using fluorescein and observing the effects of opioid peptides and interferon on the cerebral blood flow in-vivo might further strengthen the case for a specific local vascular response produced by these substances.

Work needs to be done defining the neurotransmitters of the geniculate ganglia in human subjects.

The temporal bone studies need to be repeated using specific e.g. the PA29 probe.

In conclusion it is the author's belief that the aetiology of Bell's palsy is of truly labyrinthine complexity. The evidence from this thesis is unable to dismiss HSV reactivation as a cause amongst causes of Bell's palsy but supports a multifactorial process in which humoral factors appear to be very important. It is also hoped that the hypothesis will prove of sufficient interest to merit further original investigations. The patient shown in fig. 10.9 has sadly not made a full recovery.

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APPENDICES

Appendix 1aC O N F I D E N T I A LPATIENTS WITH A PROVISIONAL DIAGNOSIS OF BELL'S (IDIOPATHIC) FACIAL PARALYSIS

Name: _____

Address: _____

Phone No: _____

Referring GP _____

Address: _____

Phone No: _____

Date _____

Age _____

Sex M _____

F _____

Occupation _____

Details of
work performed _____Work address _____

Ethnic origin:

- 1) When did you first notice your face wasn't moving properly?

on getting up or soon after approx. hrs
 round about what time hrs
 unable to say

- 2 a) Thinking back to when you first noticed you couldn't move the side of your face properly, can you remember how long before that it was working normally?

0 - 6 hrs
 6 - 12 hrs
 12 - 24 hrs
 days
 unable to say

- 2 b) For how long now have you been unable to move your face?

if possible hrs
 and days
 unable to say

- 3) If you have periods how many days do they usually last?
 How long do you go between periods?

--	--	--	--

Thinking back to the day your face was first affected can you remember where you were up to with your periods?

--	--

(1st day of period day 1) day
 unable to say

- 4) Has one side of your face been affected or both sides?

bilateral

--

If only one side, which side?

Right
 Left

Since this happened have you always been able to move the affected side of your face, at least a little? (Such as raise your eyebrow, partly close your eye, make a grimace, or move the corner of your mouth)

Yes
 No

Have you ever had anything like this before?

confirmed as a Bells palsy

Yes
 No

- 5) In the week before or after this happened had you noticed anything else the matter?
 For example have you had:

headaches at the back of your head
 pain in the ear
 a rash in or around the ear
 a dry eye
 sounds seeming abnormally loud
 numbness or loss of feeling in the face R
 L
 a 'hoarse voice'
 an abnormal feeling of movement such as the room spinning
 a burning or a flushed feeling in the face

- 6) Have you noticed that things taste differently?

Yes
 No

If yes, can you remember if this was before the weakness in the face started or after and roughly when?

days before
 12 - 24 hrs before
 6 - 12 hrs before
 0 - 6 hrs before
 more or less at the same time
 0 - 6 hrs after
 6 - 12 hrs after
 12 - 24 hrs after
 days after
 unable to say

- 7) Where applicable: Is the patient pregnant?
 or had a baby within 6 weeks of the onset of paralysis?

N/A

--

If yes then ask how many weeks of pregnancy or after

first trimester
 second trimester
 third trimester
 puerperium

- 8) Has anybody in the family ever had an unexplained weakness of the face - Bells palsy?

No ☐
 Grandparent ☐
 parent ☐
 sibling ☐
 child ☐
 other relative ☐

- 9) Are you taking any of the following medicines?

a water tablet ☐
 tablets for arthritis ☐
 a "painkiller" ☐
 fortal (pentazocine) ☐
 chlorpropamide ☐
 (for diabetes) ☐

- 10) If you have taken fortal before, was it effective in relieving pain?

N/A ☐
 Yes/No ☐

- 11) Are you a known diabetic?

Yes/No ☐

- 12) If yes do you need to take insulin or not?

Yes/No ☐

- 13) Do you know if anyone in the family has had diabetes?

Yes/No ☐

If yes did they need to take insulin (an injection) or not?

Grandparent ☐
 parent ☐
 sibling ☐
 child ☐
 other relative ☐

(1 - insulin dependant)
 2 - N.I.D.D.
 3 - unable to say)

- 14) Have you ever suffered from any other illnesses?

Have you ever had any of the following? ☐
 an inflamed pancreas? ☐
 Menières disease - a balance and hearing disorder? ☐
 migraine? ☐
 multiple sclerosis? ☐
 schizophrenia? ☐
 asthma? ☐
 a drink problem? ☐
 heart trouble? ☐
 gland trouble e.g. thyroid? ☐
 a rare hormone disease? ☐
 painful ulcers of the genitals? ☐
 ulcers of the mouth? ☐
 high blood pressure? ☐

- 15) In the month before your face became affected how much more emotional strain did you feel you were under?

would you say less strain than normal ☐
 about the normal amount ☐
 more than normal ☐
 much more than normal ☐

- 16) In the 3 months before your face was affected would you say you felt depressed? (Feeling low with a low image of yourself with a poor appetite or weight loss or sleeping difficulties).

Yes/No ☐

- 17) If yes have you needed treatment from your doctor for this?

Yes/No ☐

- 18) In the 2 weeks before your face was affected had you undertaken more physical exercise or work than usual?

Yes/No ☐

- 19) In the day or two before the face was affected can you remember if you were out in very bright sunshine?

Yes/No ☐

- 20) When you go out into the sun for any length of time
do you tend to
- burn easily? ☐
burn more than you tan? ☐
tan more than you burn? ☐
tan easily? ☐
- 21) The day prior to the face becoming affected
can you remember if you
- had you been in cold conditions causing chilling? ☐
- or been in a draught? ☐
- or consumed alcohol? ☐
- 22) Have you ever suffered from whitlows
- painful swellings on the fingers usually near the nails? Yes/No ☐ ☐
- 23) Do you bite your nails? Yes/No ☐ ☐
- 24) Do you smoke Yes/No ☐ ☐
- 25) In the two weeks before your face was affected can you
remember did you suffer
- from an illness with a temperature? ☐
a cough, cold, or chest infection? ☐
a sore throat? ☐
- 26) Can you remember ever having suffered from painful
lips and gums which were swollen and red?
- Y/N/U ☐ ☐ ☐
- 27) If yes can you remember how old you were?
- a child ☐
a teenager ☐
over 20 yrs old ☐
unable to say ☐
- 28) How recently was this?
- less than 6 months ago ☐
longer than 6 months ago ☐
longer than 5 years ago ☐
unable to say ☐
- 29) Have you ever suffered from cold sores?
A tender red patch of skin around the edge of the
lip often containing a little straw coloured fluid
(see photograph)
- Y/N/U ☐ ☐ ☐
- 30) If you suffer from cold sores can you remember
when you first started with them?
- as a child ☐
as a teenager ☐
over 20 yrs old ☐
unable to say ☐
- 31) Can you remember when you last had a cold
sore?
- in the 2 weeks before ☐
the face was affected. ☐
in the previous 6 months ☐
longer than 6 months ☐
unable to say ☐
- 32) Do the cold sores affect?
- only the left side ☐
mostly the left side ☐
the middle or both sides ☐
mostly the right side ☐
only the right side ☐
unable to say ☐
- 33) Have you recently kissed anyone with cold sores? Y/N/U ☐ ☐ ☐

Clinical examinationENT examinationneck examination

Is there clinical evidence of polyneuropathy?

Diagnosis confirmed:

Hospital referral:

Hospital admission:

Blood for antibodies (HSV) taken

Day after paralysis treatment commenced

Type of treatment:

Final outcome:

Date:

5th _____

9th gag reflex _____

10th cord immobility _____

8th/calorics _____

other cranial nerves _____

YES _____

NO _____

YES _____

NO _____

YES _____

NO _____

Day _____

Day _____

None _____

steroids _____

ACTH _____

other _____

Complete recovery _____

incomplete recovery _____

synkinesia _____

loss of power _____

crocodile tears _____

impaired taste _____

hyperacusis _____

other _____

Comments

Photographs

CONFIDENTIAL

CONTROLS FOR BELLS PALS

STUDY

Name: _____

Date _____

Age _____

Sex M

Sex F

Occupation _____

Ethnic origin:

Estimated Social Group: Group 1 _____

2 _____

3 _____

4 _____

5 _____

6 _____

- 1) In the past few days have you noticed any of the following symptoms?

headaches at the back of your head
pain in the ear
a rash in or around the ear
a dry eye
sounds seeming abnormally loud
numbness or loss of feeling in the face R
L
a 'hoarse voice'
feeling of movement such as the room spinning
a burning or a flushed feeling in the face

[illegible]

- 2) Have you noticed that recently things taste differently?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

- 3) Where applicable: Is the patient pregnant?

N/A ☐

If yes then ask how many weeks of pregnancy or after

first trimester
second trimester
third trimester
puerperium

- 4) Has anybody in the family had an unexplained weakness of the face - Bells palsy?

No	
Grandparent	
parent	
sibling	
child	
other relative	

- 5) Are you taking any of the following medicines?

a water tablet
tablets for arthritis
a "pain killer"
fortral (pentazocine)
chlorpropamide
(for diabetes)

- 6) If you have taken fortoral before, was it effective in relieving pain? N/A ☐
Yes/No ☐
- 7) Are you a known diabetic? Yes/No ☐
- 8) If yes do you need to take insulin or not? Yes/No ☐
- 9) Do you know if anyone in the family has had diabetes? Yes/No ☐
- If yes did they need to take insulin (an injection) or not? Grandparent ☐
parent ☐
sibling ☐
child ☐
other relative ☐
- (1 - insulin dependant)
2 - N.I.D.D.
3 - unable to say
- 10) Have you ever suffered from any other illnesses? Have you ever had any of the following?.....
an inflamed pancreas? ☐
Menièr's disease - a balance and hearing disorder? ☐
migraine? ☐
multiple sclerosis? ☐
schizophrenia? ☐
asthma? ☐
a drink problem? ☐
heart trouble? ☐
gland trouble e.g. thyroid? ☐
a rare hormone disease? ☐
painful ulcers of the genitals? ☐
ulcers of the mouth? ☐
high blood pressure? ☐
- 11) Thinking back over the past month how much emotional strain did you feel you were under? Would you say.....
less strain than normal ☐
about the normal amount ☐
more than normal ☐
much more than normal ☐
- 12) In the past 3 months would you say you felt depressed? (Feeling low with a low image of yourself with a poor appetite or weight loss or sleeping difficulties) Yes/No ☐
- 13) If yes have you needed treatment from your doctor for this? Yes/No ☐
- 14) Over the past 2 weeks have you undertaken more physical exercise or work than usual? Yes/No ☐
- 15) Can you remember if you were out in very bright sunshine yesterday? Yes/No ☐
- 16) When you go out into the sun for any length of time do you tend to burn easily? ☐
burn more than you tan? ☐
tan more than you burn? ☐
tan easily? ☐
- 17) Can you remember if yesterday you had - been in cold conditions causing chilling? ☐
- or been in a draught? ☐
- or consumed alcohol? ☐
- 18) Have you ever suffered from whitlows - painful swellings on the fingers usually near the nails? Yes/No ☐
- 19) Do you bite your nails? Yes/No ☐
- 20) Do you smoke? Yes/No ☐

- 21) In the past 2 weeks have you suffered from
 an illness with a temperature? ☐
 a cough, cold or chest infection? ☐
 a sore throat? ☐
- 22) Can you remember ever having suffered from painful
 lips and gums which were swollen and red? Y/N/U ☐☐☐
- 23) If yes can you remember how old you were?
 a child ☐
 a teenager ☐
 over 20 yrs old ☐
 unable to say ☐
- 24) How recently was this?
 less than 6 months ago ☐
 longer than 6 months ago ☐
 longer than 5 years ago ☐
 unable to say ☐
- 25) Have you ever suffered from cold sores?
 A tender red patch of skin around the edge of
 the lip often containing a little straw coloured
 fluid (see photograph) Y/N/U ☐☐☐
- 26) If you suffer from cold sores can you remember when
 you first started with them?
 as a child ☐
 as a teenager ☐
 over 20 yrs old ☐
 unable to say ☐
- 27) Can you remember when you last had a cold sore?
 in the 2 weeks before ☐
 the face was affected ☐
 in the previous 6 months ☐
 longer than 6 months ☐
- 28) Do the cold sores affect?
 only the left side ☐
 mostly the left side ☐
 the middle or both sides ☐
 mostly the right side ☐
 only the right side ☐
 unable to say ☐
- 29) Have you recently kissed anyone with cold sores? Y/N/U ☐☐☐

PLEASE TICK LIFE EVENTS

FAMILY	Death of spouse Divorce Marital separation Death of close family member Marriage Marital reconciliation Major change in health of family Pregnancy Addition of new family member Major change in arguments with wife/husband Son or daughter leaving home In-law troubles Wife starting or ending work Major change in family get-togethers
PERSONAL	Detention in jail Major personal injury or illness Sexual difficulties Death of a close friend Outstanding personal achievement Start or end of formal schooling Major change in living conditions Major revision of personal habits Changing to a new school Change in residence Major change in recreation Major change in church activities Major change in sleeping habits Major change in eating habits Vacation Christmas Minor violations of the law
WORK	Being fired from work Retirement from work Major business adjustment Changing to different line of work Major change in work responsibilities Trouble with boss Major change in working conditions
FINANCIAL	Major change in financial state Mortgage or loan over £10,000 Mortgage foreclosure Mortgage or loan less than £10,000

Appendix 2a

UNIVERSITY OF MANCHESTER

THE DEPARTMENT OF GENERAL PRACTICE
RUSHOLME HEALTH CENTRE
WALMER STREET
MANCHESTER M14 5NP

PROFESSOR DAVID METCALFE

TELEPHONE: 061-225 6693

June 1985

Dear Doctor,

I am writing to ask your co-operation in a unique clinical study which is being carried out by a trainee in this Department. It concerns questions regarding the nature and aetiology of Bell's palsy. We need, over the course of 12 months, to be able to see about 100 cases of this disease in order to ascertain some facts about co-existing factors and to take blood for viral studies. Dr. Williamson will visit each of the patients to ascertain these facts (by using a questionnaire) and take a sample of blood.

As you are aware, Bell's palsy is not a notifiable condition and its incidence is low (20/100,000 of the population per year). We therefore need to have the co-operation of a large number of general practitioners in the region who will notify this Department of any case of Bell's palsy which they see.

What we are asking therefore is whether you will agree to help by:-

- 1) Notifying (by telephone or letter) this Department of any case of Bell's palsy seen in the next 12 months;
- 2) Agreeing that Dr. I.G. Williamson (trainee GP) may visit your patient for the purpose of completing a questionnaire and taking a blood sample.

The patient's permission would be sought before the interview and you would be sent copies of the completed questionnaire and viral studies report. The work involved by you will be minimal, in fact only notification, but the overall results may be a significant improvement in our understanding of a condition which sometimes results in permanent disfigurement.

I enclose an outline of the study and will also send you a copy of the questionnaire and the references if you would like them. Please would you complete the enclosed pro forma and return it to this Department.

With very many thanks for your co-operation.

Yours sincerely,

A handwritten signature in cursive script, appearing to read 'E. Idris Williams'.

E. Idris Williams, MD FRCP
Senior Lecturer

encs:

A STUDY OF BELL'S PALSY

Introduction

Bell's palsy or idiopathic facial paralysis is essentially a diagnosis of exclusion and may represent a heterogeneous group of conditions. However there are features which suggest a common aetiological mechanism although exactly what this is remains contentious. The two most widely held theories are the viral and the vascular, although there is no reason to suppose that they are mutually exclusive. In 1972 McCormick first postulated herpes simplex as a cause for Bell's palsy and since then a number of workers have produced evidence to corroborate this theory. Adour, in San Francisco, in an extensive epidemiological study, showed a high association between patients suffering from the disease and elevated herpes simplex antibodies. It is argued by supporters of herpes simplex as a cause that reactivations of this virus often occur without demonstrable rises in antibody levels. Furthermore, most of the population of over 30 year olds already have antibodies to herpes simplex. Thus conventional clinical methods of proof are inadequate in incriminating this virus.

Herpes simplex nevertheless remains a good candidate for several reasons. Work over the past 12 years has shown a predilection of this virus for neural tissue and primary afferent sensory ganglia in particular. Krisstensen (1977) has shown in animal models that the virus produces local demyelination similar to that seen in Bell's palsy. Reactivation of herpes infection is thus problematical in terms of proof and epidemiological studies remain the only way of confirming such a hypothesis. Direct biopsy of the facial nerve is not an ethical alternative. Isolating the virus from cadaveric geniculate ganglia might be a possibility and this is being pursued.

Vascular theories are also held by many clinicians including Kettel, Cawthorne and Janetta. In support of these are the abrupt onset of paralysis and the discrete anatomical localisation of nerve damage. Fisch proposes that the nerve damage is produced by a viral vasoactive toxin. The interesting point of this idea is not so much that viruses do not produce toxins, but that interferon and the neuro-transmitters found in the geniculate ganglion (opioid peptides) are vasoactive and may mediate vascular damage (Scott; Hanko). A considerable amount of work has been done in this field, particularly by Blalock and Smith, and all within the past five years. Both interferons and opioid peptides have very short half-lives in plasma, which means that serum levels are not true indicators of local processes where the concentration level may be marked. It is known that such factors as age, circadian rhythm, emotional stress, cold stress, menstruation, pregnancy, drugs, endocrine disorders, all alter the bodies 'opioid' status. A condition which is known to be associated with sensitivity to opioid peptides is non-insulin dependent diabetes, a disease in which Bell's palsy often occurs. A study of a reasonably large number of cases of Bell's palsy to determine associations between the disease and any of the above opioid sensitive factors would therefore be interesting and if associations were present would provide new evidence for the vascular 'toxic' theory.

Purpose of Study

The purpose of the study is to determine whether in Bell's palsy there is an increased incidence of certain factors which are known to increase the bodies opioid sensitivity. This will be achieved by collecting, in the North West region, 100 cases of Bell's palsy presenting to their general practitioners and comparing them with an equal number of randomly sampled controls matched for age, sex, social class and geographical area.

Fundamental Hypothesis

That Bell's palsy (idiopathic facial) is produced as a result of a neural reactivation of herpes simplex virus persistent in the geniculate ganglion. This results in an activation of the interferon/opioid system resulting in high, but localised, concentrations of these vasoactive substances. The resultant vasodilation causes neuro-praxia to the facial nerve, and where anatomical factors conspire to produce irreversible ischaemic changes in the nerve.

This study is aimed at demonstrating the increased likeliness of this reactivation and vascular 'toxic' effect in certain specific opioid sensitive situations.

Incidence

The most frequently quoted figure for incidence of this condition in Western Europe is 20/100,000 per year.

Logistics

- 1) The study will involve the collection of 100 cases of Bell's palsy over the course of one year. This will involve drawing from a population base of 500,000 patients.
- 2) To achieve this it will be necessary to recruit 250 general practitioners in the region who are prepared to notify all their cases of Bell's palsy to the researcher within this Department.
- 3) When the case has been notified the researcher will visit each patient to fill in a questionnaire and take a small sample of blood for viral antibody studies.
- 4) A further 100 patients will serve as matched controls and will answer the appropriate questions in the same questionnaire. The exact method of recruiting these study patients has yet to be ascertained.

Appendix 2bReply Slip to First Letter

Please TICK the appropriate boxes

I agree to notify Bell's palsy patients
during the next year

☐

I do not agree to notify Bell's palsy
patients during the next year

☐

I require stamped addressed envelopes
for the purpose of this notification

☐

I do not require stamped addressed
envelopes for the purpose of this
notification

☐

from: Dr. _____
(please print)

address: _____

PLEASE RETURN THIS FORM TO:-

Dr. E.I. Williams
Department of General Practice
University of Manchester
Rusholme Health Centre
Walmer Street
Manchester M14 5NP



UNIVERSITY OF MANCHESTER

THE DEPARTMENT OF GENERAL PRACTICE
RUSHOLME HEALTH CENTRE
WALMER STREET
MANCHESTER M14 5NP

PROFESSOR DAVID METCALFE

TELEPHONE: 061-225 6699

March 1986

Dear Doctor,

This is a reminder about the Bell's palsy study.

Thank you for your continued interest and help. 253 general practitioners in the Greater Manchester area are participating, giving a population base of approximately half a million. So far 50 cases of Bell's palsy have been admitted to the study and preliminary analysis of the data shows interesting epidemiological evidence, thus far consistent with a 'herpes simplex reactivation model' as a cause. There is an apparent increase in incidence in North Manchester regions, eg Middleton, and the incidence in North Manchester as a whole appears to be three or four times that of South Manchester. We are of course very anxious to make sure that this is a real difference, and not merely due to doctors forgetting to notify cases, so as to obtain a true picture of the incidence in a defined population during the study period.

Could you therefore complete and return the attached sheet which will provide some further information for analysis. If you have already reported a case of Bell's palsy to the Department, thank you for doing so. Such cases will be followed up at six months from the onset to allow other possible (but unlikely) pathology to present itself, and to allow clearer assessment of outcome.

Yours sincerely,

Dr. I.G. Williamson

enc:

NAME OF PRACTITIONER _____ Date _____

1. My list size is _____

2. My FPC area is (eg Stockport, Rochdale, etc) _____

3. I have reported all new cases of Bell's palsy since notification (June-August 1985)

☐

Yes

☐

No

4. If NO, then:-

a) there have been cases but I cannot remember details

☐

b) the patient did not wish referral

☐

The details of the case(s) are:-

Name _____

Name _____

Address _____

Address _____

Phone no _____

Phone no _____

Approx onset _____

Approx onset _____

5. I have reported a case which was on my partner's list

☐

Yes

☐

No

Name of partner _____

6. I will continue to report all new cases of Bell's palsy to the Department (no patient has been seen against his/her wishes) until the end of the study period - July 31st 1986☐

Yes

☐

No

Appendix 2e

UNIVERSITY OF MANCHESTER

THE DEPARTMENT OF GENERAL PRACTICE
RUSHOLME HEALTH CENTRE
WALMER STREET
MANCHESTER M14 5NP

PROFESSOR DAVID METCALFE

TELEPHONE: 061-225 6693 Ext.

February 1987

CONFIDENTIAL

Dear

I am extremely grateful for your co-operation in the Bell's Palsy Study. The information collected should indeed be very valuable. Before this information is processed on the computer however I would be grateful if you could complete the following short questionnaire:

Has the face now fully recovered? (please tick)

- | | |
|------------------------|--------------------------|
| 1) Complete recovery | <input type="checkbox"/> |
| 2) Incomplete recovery | <input type="checkbox"/> |

If INCOMPLETE, is there:

- | | |
|----------------------------------|--------------------------|
| 1) Loss of power | <input type="checkbox"/> |
| 2) Abnormal movements | <input type="checkbox"/> |
| 3) Crocodile tears | <input type="checkbox"/> |
| 4) Impaired taste | <input type="checkbox"/> |
| 5) Abnormal loudness
of sound | <input type="checkbox"/> |
| 6) Other | <input type="checkbox"/> |

Thank you again for your co-operation.

Yours sincerely,

Ian Williamson MB ChB MRCP FRCS

APPENDIX 3aList of Family Practitioner Committees Participating in Study

Mr. Thomas
Bolton FPC
43 Churchgate
Bolton.

Mr. N. Greenwood
Bury FPC
22a Union Arcade
Bury BL9 0QF.

Mr. E.W. Sykes
Rochdale FPC
Telegraph House
Baillie Street
Rochdale OL16 1LJ.

Mr. N. Chester
Salford FPC
The Willows
Lords Avenue
Salford M5 2JR.

Mr. W. Jones
Manchester FPC
2a Higher Ardwick
Manchester M12 6BX.

Mr. G. Evans
Oldham FPC
St. Peter's House
Oldham OL1 1JL.

Mr. A. Jones
Stockport FPC
Burley House
1 Marriott Street
Higher Hillgate
Stockport SK1 3PP.

Mr. B.E. Thomas
Tameside FPC
Woodhead House
44/46 Market Street,
Hyde SK14 1AH.

Appendix 3bList of Participating G.P.'s

Names and addresses of 252 participating general practitioners.
 * denotes a positive response to the reminder letter at 8 months.
 The number of cases reported by each G.P. is also given.

Dr. H.W.K. Acheson
 Department of General Practice
 Rusholme Health Centre.

Dr. V.P. Addis
 Whitefield Health Centre
 Bury New Road
 Whitefield
 MANCHESTER M25 6GH.
 *

Dr. J. Agarwala
 523 Liverpool Road
 Irlam
 Manchester M30 6BH.

Dr. M. Alam
 Heaton Norris Health Centre
 Short Street
 STOCKPORT SK4 1SX.

Dr. S. Alam
 Mosley Health Centre
 Market Street
 MOSSLEY.

Dr. A. Allan
 10 Broadgate
 Ladybridge
 BOLTON.

Dr. M. Allan
 Heaton Norris Health Centre
 Cheviot Close
 Stockport
 Cheshire.

Dr. J.A. Ambrose
 379 Greenbrow Road
 NEWALL GREEN
 Wythenshawe.

Dr. R. Apte
 523 Liverpool Road
 Irlam
 MANCHESTER M30 6BH.

Dr. W.D. Ashworth
 The Smithy
 4 Market Street
 HOLLINGWORTH
 Hyde
 Cheshire.

Dr. K.K. Balayogi
 Craven Street,
 DROYLSDEN.

Dr. S. Bailey
 The Surgery
 Block Lane
 CHADDERTON
 Oldham.

Dr. D. Barlow
 2 Edward Street
 OLDHAM OL9 7QW.

Dr. D.C. Bayman
 The Health Centre
 Ashton Road West
 FAILSWORTH M35 OHN.

Dr. M.J. Beard
 Royton Health Centre
 Rochdale Road
 ROYTON
 Oldham.

Dr. D. Jane Bell
 2 Bleak Hey Road
 MANCHESTER M22 5ES.
 *

Dr. I.J. Benett
 Hulme House
 Royce Road
 MANCHESTER M15.
 *

Dr. D.G. Bennett
 Clarendon House
 HYDE
 Cheshire.
 *

Dr. P.W. Bennett
 Clarendon House
 Clarendon Street
 HYDE
 Cheshire.

Dr. W.G. Bennett
 Donneybrook House.
 Clarendon Street
 HYDE
 Cheshire SK14 2AH.

Nr. N.C. Beriwal
 The Health Centre
 Market Place
 MOSSLEY
 Lancs OL5 OHE.
 *

Dr. J.M. Bernstein
 The Surgery
 53-55 Crescent Road
 MANCHESTER M8 7JT.

Dr. Bhatt
 The Surgery
 Simmondley
 Glossop.
 *

Dr. D. Bora
 Avondale Health Centre
 Avondale Street
 BOLTON.
 *

Dr. Borkin
 Eccles Health Centre
 ECCLES
 Manchester M30 0EQ.
 *

Dr. Joyce Bourne
 Clarendon Surgery
 72 Denbigh Place
 SALFORD M5 4BE.
 *

Dr. M.C. Brady
 Springfield House
 275 Huddersfield Road
 OLDHAM.
 *

Dr. P.F. Brien
 212 Eccles Old Road
 Salford 6.
 * 1 case

Dr. A.L. Brown
 Rusholme Health Centre.
 * 2 cases

Dr. S.M. Brown
 Capital Road Surgery
 HIGHER OPENSHAW
 Manchester M11 1LA.

Dr. D. Bunting
 Richmond Group Practice
 Crickets Lane Health Centre
 ASHTON-UNDER-LYNE
 Lancs.

Dr. A. Cahill
 Cheadle Medical Practice
 1-3 Ashfield Crescent
 CHEADLE
 Cheshire.

Dr. B.M. Caldwell
 Wellfield Surgery
 291 Oldham Road
 ROCHDALE.
 *

Dr. P. Callow,
 2 Edward Street,
 WERNETH
 Oldham
 Lancs.
 *

Dr. T.G.S. Cameron
 15 Bridge Street
 Heywood
 Lancs.
 *

Dr. Capek
 216 Wythenshawe Road,
 Northern Moor
 MANCHESTER M23 OPH.

Dr. J. Cassidy
 Ann Street Health Centre
 DENTON
 Tameside.

Dr. J.M. Chang
 Shaw Heath Health Centre
 Gilmore Street
 STOCKPORT.

Dr. P.J.L. Chapman
 Heald Green Health Centre
 Finney Lane,
 HEALD GREEN
 Cheadle.

Dr. C.Y. Cheong
 12 Vernon Road
 Greenmount
 BURY.

- Dr. S. Child
Woodbank Surgery
2 Hunstanton Drive
BURY
Lancs BL8 1EG.
*
- Dr. S.K. Chouksey
Group Practice Centre
Hulme House
Royce Road
MANCHESTER M15 5FR.
*
- Dr. H.R. Chowdhury
Lower Broughton Health Centre
SALFORD M7 9RN.
*
- Dr. R. Clark
25 Mottram Moor
MOTTRAM
Cheshire.
- Dr. G. Clarke
Mossley Road
ASHTON
Manchester.
*
- Dr. P.J. Cleator
41 Manchester Road
WALKDEN
Manchester M28 5WS.
*
- Dr. D. Clynes
Higher Broughton Health Centre
Bevendon Square
SALFORD M7 0UF.
- Dr. Eva Clynes
10 Daneshill
PRESTWICH
Manchester M25 5GJ.
*
- Dr. M.P. Clynes
Higher Broughton Health Centre
Bevendon Square
SALFORD M7 0UF.
- Dr. D.R. Cole
Minden Medical Centre
Minden Parade
BURY
Lancs.
* 1 case
- Dr. M.M. Cooper
Kildonan House
Horwich
Bolton BL6 5NW.
*
- Dr. J.H. Couper
Levenshulme Health Centre
Dunstable Street
MANCHESTER M19 3BX.
*
- Dr. D.M. Couper
283 Hollyhedge Road
Wythenshawe
MANCHESTER 22.
- Dr. R.A. Cranna
Dunscar Health Centre
Darwen Road
BROMLEY CROSS
Bolton BL7 9RG.
* 1 case
- Dr. A.J. Crook
Wellfield Surgery
291 Oldham Road
ROCHDALE.
- Dr. Judith Curran
Chorlton Health Centre
1 Nicolas Road
CHORLTON
Manchester 21.
- Dr. V.R. Dalal
53 Durnford Street
MIDDLETON
Manchester M24 3TZ.
*
- Dr. W.C. Davidson
Brunswick Health Centre
Hartfield Close
MANCHESTER M13 9TP.
- Dr. J. Davies
Rusholme Health Centre.
- Dr. N.J. Dawes
70 Spotland Road
ROCHDALE
Lancs.
1 case
- Dr. C.A. Day
262 Stockport Road
CHEADLE HEATH
Stockport
Cheshire.
- Dr. J.F. Day
The Health Centre
Smithy Green
CHEADLE HULME
Cheshire SK8 6LU.
- Dr. G. Dean
'Tregenna'
Portway
MANCHESTER M22 6EP.
* 2 cases
- Dr. A. Demetriou
The Minden Medical Centre
7 Minden Parade
BURY BL9 0QG.
1 case
- Dr. D. Dench
Failsworth Health Centre
Ashton Road West
FAILSWORTH
Nr. Manchester.
*
- Dr. D.L. Dennard
Cannon Street Health Centre
BOLTON BL3 5TA.
*
- Dr. M.J. Derbyshire
523 Liverpool Road
IRLAM
Nr. Manchester.
*
- Dr. Dimery
The Health Centre
LITTLEBOROUGH
Lancs.
- Dr. M.J. Dobson
50 Church Street
MARPLE
Stockport SK6 6BW.
* 1 case
- Dr. M.C. Donaghy
The Health Centre
Smithy Green
CHEADLE HULME
Cheshire.
* 1 case
- Dr. O.M. Duddy
St. Gabriel's Medical Centre
4 Bishops Road
PRESTWICH
Manchester M25 8HT.
*
- Dr. P. Element
10 Hodge Road
WORSLEY
Manchester M28 5AT.
*
- Dr. B. Epstein
Clarendon Surgery
72 Denbigh Place
SALFORD M5 4BE.
- Dr. M.S. Erram
Lower Broughton Health Centre
Great Clowes Street
SALFORD M7 9RN.
- Dr. J. Everett
The Hollies
Oxford Road
DUKINFIELD
Cheshire SK16 5PQ.
*
- Dr. G. Fairbairn
1 Vicars Drive
ROCHDALE
Lancs
* 1 case
- Dr. Fairlie
379 Greenbrow Road
MANCHESTER 23.
- Dr. D.I. Fleming
The Health Centre
Cannon Street
OLDHAM
Lancs.
- Dr. Fletcher
Astley Bridge Health Centre
10 Moss Bank Way
BOLTON BL1 8NP.
*
- Dr. M.S. Fletcher
Dunscar Health Centre
Darwen Road
BROMLEY CROSS
Bolton BL7 9RG.
- Dr. B.D. Ford
Glodwick Health Centre
Glodwick Road
OLDHAM
Lancs.
- Dr. B.V. Fredrick
Failsworth Health Centre
Ashton Road West
FAILSWORTH
Manchester.
- Dr. F. Freedman
Northenden Health Centre
489 Palatine Road
NORTHENDEN
Manchester M22 4DH.

Dr. W.S. Furniss
Woodley Health Centre
WOODLEY
Stockport SK6 1NB.

Dr. F. Galea
36 Rawsen Street
FARNWORTH
Bolton
Lancs BL4 7RJ.
*

Dr. N.K. Ghosh
Woodbank Surgery
2 Hunstanton Drive
BURY
Lancs BL8 1EG.
*

Dr. Mary Gibbs
177 Mauldeth Road
MANCHESTER 14.
*

Dr. J.A. Gibson
15 Bridge Street
HEYWOOD
Lancs.
*

Dr. J. Glass
Longsight Health Centre
528 Stockport Road
MANCHESTER M13 0WR.
* 1 case

Dr. S.E. Glass
302 Errwood Road
BURNAGE
Manchester M19 1DX.
*

Dr. R.E. Goodman
101 Manchester Road
DENTON
Manchester M34 2AF.

Dr. N. Gowri
17 The Strand
KIRKHOLT
Rochdale
Lancs OL11 2JG.
*

Dr. A.S. Grieve
'Tregenna'
Portway
MANCHESTER M22 6EP.
*

Dr. R. Hague
50 Acres Lane
STALYBRIDGE
SK15 2JU.
*

Dr. B.P. Halder
48 Turks Road
RADCLIFFE
Manchester.
*

Dr. C.E. Hall
The Health Centre
Cannon Street
BOLTON.
*

Dr. R.G. Hall
Lance Burn Health Centre
Churchill Way
SALFORD M8 5AU.

Dr. K. Hardy
Littleborough Health Centre
off Featherstall Road
LITTLEBOROUGH
Lancs.

Dr. M. Harrington
Milnrow Health Centre
1 Stonefield Street
MILNROW
Lancs.
* 1 case

Dr. B.V. Harris
Melbourne House
1 Stoneclough Road
KEARSLEY
Bolton.
* 1 case

Dr. P. Harris
West Gorton Medical Centre
6a Wenlock Way
MANCHESTER M12 5LH.
*

Dr. A. Hart
250 Langworthy Road
SALFORD M6 5WW.
1 case

Dr. I.T. Heathcote
48a Rochdale Road
MIDDLETON.
* 1 case

Dr. P.J. Hedley
50 Church Street
MARPLE
Stockport SK6 6BW.
*

Dr. S.J. Henderson
127 Woodhouse Lane
MANCHESTER 22.
*

Dr. H.C. Henry
Hulme House
MANCHESTER M15 5FR.
*

Dr. C.A. Higgins
Sudden Health Centre
Silk Street
SUDDEN
Rochdale OL11 3EU.

Dr. A.S. Hill
127 Woodhouse Lane
MANCHESTER M22 7WP.
*

Dr. J.B. Hill
49 Fairfield Square
DROYLSDEN
Manchester M35 6BT.

Dr. K. Holland-Elliott
Clarendon Surgery
72 Denbigh Place
SALFORD M5 4BE.

Dr. J.A. Holt
Minden Medical Centre
7 Minden Parade
BURY.
*

Dr. J.E. Horrocks
Wellfield Surgery
211 Oldham Road
ROCHDALE OL16 5HX.

Dr. D.J. Hudson
70 Spotland Road
ROCHDALE
Lancs.
*

Dr. M. Hunt
9 Brandlesholme Road
Greenmount
BURY BL8 4DR.

Dr. Z. Hussain
Moss Side Health Centre
Monton Street
MANCHESTER M14.

Dr. G.P. Ibbotson
Baillie Street Health Centre
ROCHDALE
Lancs.

Dr. D.K.F.H. Jackson
56 Higher Hillgate
STOCKPORT SK1 3PZ.
*

Dr. I.G.V. James
555 Chorley Old Road
BOLTON BL1 6AF.
*

Dr. J.M. James
Monton GP Practice
267 Monton Road
MONTON
Eccles.

Dr. Milton Jeffries
The Medical Centre
825 Manchester Road
BLACKFORD BRIDGE
Bury BL9 9HB.

Dr. S. Jenkins
Minden Medical Centre
7 Minden Parade
BURY BL9 0QG.
*

Dr. G. Jessup
24 Braintree Road
Wythenshawe
Manchester 22.

Dr. M.A. Johnson
The Clinic
Smithy Lane
UPPERMILL,
Nr. Oldham.

Dr. R. Johnson
171 Manchester Road
MOSSLEY
Ashton-under-Lyne OL5 9AB.

Dr. B.P. Jones
6 Hodge Road
Worsley
MANCHESTER M28 5AT.
*

Dr. M. Jones
76 Stockport Road
MARPLE
Cheshire SK6 6AH.

Dr. N. Joseph
The Minden Medical Centre
7 Minden Parade
Bury BL9 0QP.
* 1 case

Dr. R.C. Joshipura
58 Rochdale Road
MANCHESTER M10 7GT.

Dr. P.F. Kallis
363 Wilmslow Road
FALLOWFIELD
Manchester M14 6XU.

Dr. T.F. Kean
284 Lees Road
OLDHAM.

Dr. J.S. Kelly
Royton Health Centre
Rochdale Road
ROYTON
Lancs.
* 1 case

Dr. J.W. Kelso
99 High Street
LEES
Oldham OL4 4LY.
*

Dr. M. Kelvin
Gorton Medical Centre
46 Wellington Street
MANCHESTER M18 8LI.
*

Dr. A.G. Kennedy Young
Bramhall Health Centre
Bramhall Lane South
BRAMHALL
Cheshire.

Dr. I.F.W. Kerr
Penny Meadow Clinic
Ashton-Under-Lyne
Lancs.

Dr. K.L. Khan
Moss Side Health Centre
Monten Street
MANCHESTER M14 4GP.

Dr. S. Kokiet
Penny Meadow Clinic
Glebe Street
Ashton-Under-Lyne
Lancs.

Dr. I. Kopman
South Chadderton Health Centre
Eaves Lane
CHADDERTON
Lancs.

Dr. D.G. Larah
Higher Broughton Health Centre
Bevendon Square
SALFORD M7 0UF.

Dr. J.B. Law
Whitefield Health Centre
Bury New Road
WHITEFIELD
Manchester M25 6GH.

Dr. G. Leach
267 Monton Road
ECCLES
Manchester M30 9LF.
* 2 cases

Dr. S.B. Lester
213 Chestergate
STOCKPORT SK3 0AP.

Dr. M. Levi
8 Pensby Walk
Queens Road
MANCHESTER M10 8GN.
*

Dr. B. Lewis
Sudden Health Centre
Silk Street
ROCHDALE OL11 3EU.
*

Dr. J. Lewis
Bramhall Health Centre
BRAMHALL
Cheshire.
*

Dr. R. Littlewood
Cannon Street Health Centre
Cannon Street
BOLTON
Lancs.
*

Dr. B.K. Loomba
The Health Centre
Carr Street
RAMSBOTTOM
Bury.
*

Dr. S.A. MacKenzie
173 Mauldeth Road
FALLOWFIELD
Manchester 14.
*

Dr. D.N. MacKinnon
Deansgate Health Centre
Bolton
LANCS BL1 1JE.

Dr. I. MacLellan-Smith
1-3 Ashfield Crescent
CHEADLE
Cheshire.
*

Dr. T.V. Maher
439 Mill Street
MANCHESTER M11 2BL.
*

Dr. P.G. Mann
The Health Centre
Frederick Street
FARNWORTH
Bolton BL4 9AH.

Dr. J.E. Marginson
68 Worsley Road
WORSLEY
Nr. Manchester.
*

Dr. P.E. Mark
32/34 Rowan Close
SALFORD 6.
*

Dr. B.E. Marks
Rusholme Health Centre.
*

Dr. K.C. Marshall
262 Stockport Road
CHEADLE HEATH
Stockport
Cheshire.
* 1 case

Dr. C. Martin
32 Burton Road
Withington
MANCHESTER M20 9EB.
1 case

Dr. G. Mathew
Heady Hill House
Heep Lane
HEYWOOD
Lancs.
*

Dr. J.A. Maudar
Peterloo Medical Centre
133 Manchester Old Road
MIDDLETON
Manchester M24 4DZ.

Dr. V.B. Maxwell
Gatley Health Centre
Old Hall Road
GATLEY
Cheshire.
*

Dr. C. McIntosh
The Surgery
Block Lane
CHADDERTON
Oldham.
*

Dr. G. McLardy
Halliwell Health Centre
Aylesford Walk
BOLTON BL1 3SQ.
*

Dr. A.F.F. McLean
645 Wilmslow Road
DIDSBURY
Manchester M20 0BA.

Dr. B. Miller
70 Spotland Road
ROCHDALE.
1 case

Dr. P.I. Miller
Shaw Heath Health Centre
Gilmore Street
STOCKPORT SK3 8DN.
* 1 case

Dr. P. Milner & A. Asthana
189 King Street
DUKINFIELD
Cheshire.

Dr. J.E. Milson
Alvanley Clinic
1 Auburn Avenue
BREDBURY
Nr. Stockport.

Dr. H.A. Mitchell
5 Lowfield Road
STOCKPORT SK2 6RW.

Dr. R.G. Mitchell
Deansgate Health Centre
BOLTON BL1 1JE.

Dr. E.A. Mkandawire
4 Collinge Street
SHAW
Oldham OL2 8AA.
*

Dr. D. Mohammad
Lower Broughton Health Centre
SALFORD M7 9RN.
*

Dr. B. Molyneaux
Whitefield Health Centre
Bury New Road
WHITEFIELD
Manchester M25 6GH.

Dr. A.M. Molyneaux
Whitefield Health Centre
Whitefield
Nr. Manchester.
* 1 case

Dr. R.J. Morgan
1 Ashfield Crescent
CHEADLE
Cheshire.
*

Dr. J.O. Moysey
"Donneybrook House"
HYDE
Cheshire.
1 case.

Dr. A. Naeem
507 Whitworth Road
ROCHDALE
Lancs.

Dr. J.P. Nagle
Dalton House Surgery
Leigh Road
WESTHOUGHTON
Bolton
Lancs.

Dr. V. Nammalwar
62 Mount Road
ALKRINGTON
Middleton.
*

Dr. I. Napier
Donneybrook House
Clarendon Street
HYDE
Cheshire.
*

Dr. E. Needham
Richmond Group Practice
Crickets Lane Health Centre
Crickets Lane
ASHTON-UNDER-LYNE OL6 6NG.
*

Dr. Neiningner
Woodbank Surgery
2 Hunstanton Drive
BURY
Lancs BL8 1EG.
* 1 case

Dr. M. Nelson
262 Stockport Road
CHEADLE HEATH
Stockport
Cheshire.
*

Dr. B. Newgrosh
Great Lever Health Centre
Rupert Street
BOLTON.
* 1 case

Dr. J.A.H. Nicholson
Halliwell Health Centre
Aylesford Walk
BOLTON BL1 3SQ.

Dr. Nield
Heaton Norris Health Centre
Cheviot Close
HEATON NORRIS
Stockport.
*

Dr. E.A. Noronha
56 Hodge Road
WALKDEN
Worsley
Nr Manchester.
* 2 cases

Dr. B.J. O'Driscoll
2 Capital Road
Higher Openshaw
Manchester M11 1LA.
*

Dr. Jean Ormerod
54 Braintree Road
Wythenshawe
Manchester 22.

Dr. A.O. Osbaldeston
Royton Health Centre
ROYTON
Lancs.
*

Dr. S.K. Pal
Royton Health Centre
Rochdale Road
ROYTON
Oldham.
* 2 cases

Dr. M.R. Parashchak
15 Bridge Street
HEYWOOD
Lancs.

Dr. K.R. Patel
Pennymeadow Clinic
Glebe Street
ASHTON-UNDER-LYNE
Lancs.

Dr. B.A. Pattoo
126 Bollington Road
Manchester M10 7HN.
1 case

Dr. R. Peck
The Surgery
Wood Street
LANGLEY
Middleton
Manchester.
2 cases

Dr. W.J. Pettit
2 Bleak Hey Road
Peel Hall
Wythenshawe
Manchester M22 5ES.

Dr. Hazel Platts
Spotland Surgery
70 Spotland Road
ROCHDALE
Lancs.
*

Dr. T.S. Platts
Sudden Health Centre
Silk Street
SUDDEN
Rochdale.
*

Dr. R.M. Price
Blackburn St. Health Centre
RADCLIFFE
Manchester M26 9WS.
*

Dr. H.M. Purser
Shaw Heath Health Centre
Gilmore Street
STOCKPORT.

Dr. J.S. Randhawa
283 Hollyhedge Road
Wythenshaw
MANCHESTER M22 4QR.
*

Dr. U. Rao
Grosvenor Medical Centre
STALYBRIDGE
Cheshire.
* 1 case

Dr. R.H. Rathi
Beswick Health Centre
Ranworth Close
BESWICK
Manchester 11.
*

Dr. R.J. Rhodes
Crickets Lane Health Centre
ASHTON-UNDER-LYNE
Lancs OL6 6NG.

Dr. J.K. Rout
1 Stoneclough Road
KEARSLEY
Bolton BL4 8ED.
* 2 cases

Dr. P. Rowlands
70 Spotland Road
ROCHDALE
Lancs.
*

Dr. O. Rvmaszewski
Glodwick Health Centre
OLDHAM
Lancs OL4 1YN.
*

Dr. A. Saeed
Baillie Street Health Centre
Baillie Street
ROCHDALE
Lancs.
*

Dr. R. Saeed
863 Ashton New Road
CLAYTON
Manchester M11 4PB.
2 cases

Dr. S. Sahay
Lance Burn Health Centre
Churchill Way
SALFORD M6 5AU.
*

Dr. K. Samsell
Shaw Heath Health Centre
Gilmore Street
Edgeley
Stockport
Cheshire.

Dr. J.E. Sandars
Cheadle Hulme Health Centre
Smithy Green
CHEADLE HULME
Cheshire SK8 6LU.

Drs. Sandle, Flynn, Coates, Burt
Kay, Crowther and Kowk
Barlow Medical Centre
8 Barlow Moor Road
MANCHESTER M20 0TR.
*

Dr. C. Shadforth
Littleborough Health Centre
Featherstall Road
LITTLEBOROUGH
Lancs.

Dr. M.S. Shah
Al Kowsar Surgery
102 Werneth Hall Road
OLDHAM OL8 4BD.
*

Dr. S. Shaw
Tonge Moor Health Centre
Ticketford Road
BOLTON
Lancs.
*

Dr. D.B. Shaw
'Tregenna'
Portway
MANCHESTER M22 6EP.
*

Dr. K. Shearer
52 Bowland Road
Baguley
Manchester 23.

Dr. C. Shekar
The Minden Medical Centre
7 Minden Parade
BURY
Lancs.
*

Dr. A.D. Shepherd
Heaton Moor Health Centre
32 Heaton Moor Road
HEATON MOOR
Stockport.
* 1 case

Dr. D. Shlosberg
36 St. Bee's Close
Denmark Road
MANCHESTER M14 4GG.
*

Dr. B.A. Sides
'Windward'
68 Worsley Road
WORSLEY
Manchester M28 4SN.
*

Dr. T. Sinclair
The Clinic
Smithy Lane
UPPERMILL
Oldham OL3 6AJ.
*

Drs. Smith, Sheppard, Momen
& McGrogan
51 Victoria Avenue
BLACKLEY
Manchester 9.

Dr. J. Smith
141 Buxton Road
STOCKPORT
Cheshire SK2 6EQ.

Dr. B.J. Sopher, J. Hayden
and M.L. Mattison
Unsworth Medical Centre
Parr Lane
BURY BL9 8JR.
*

Dr. Sarah Styler
Peel Health Centre
Market Street
BURY.

Dr. J.P. Sydney
Marjory Lees Health Centre
Egerton Street
OLDHAM
Lancs.
*

Dr. T. Tauk
Hulton District Health Centre
Haysbrook Avenue
LITTLE HULTON
Worsley.

Dr. A.W. Taylor
99 High Street
LEES
Oldham OL4 41Y.
*

Dr. D.B.S. Taylor
Cannon St. Health Centre
Cannon Street
BOLTON
Lancs.
*

Dr. M.B. Taylor
40 Market Street
HEYWOOD
Lancs.
* 1 case

Dr. Thornton
594 Altrincham Road
MANCHESTER M23 9JH.

Drs Tingley & Trimm
494 Liverpool Street
SALFORD 6.

Dr. M.J. Travenen
24 Longshut Lane West
STOCKPORT.
*

Dr. Treacy
267 Monton Road
ECCLES
Manchester.
1 case

Dr. E.F. Unwin
473/5 Princess Road
WITHINGTON
Manchester 20.

Dr. Wakefield
Deansgate Health Centre
BOLTON BL1 1JE.
* 1 case

Dr. F.H. Walker
Pendlebury Health Centre
PENDLEBURY
Manchester M27 2HP.

Dr. J. Walker
Levenshulme Health Centre
Dunstable Street
MANCHESTER M19 3BX.

Dr. T. Ward
Laycock House
King Street
STALYBRIDGE
Cheshire SK15 2AE.
*

Dr. W.B. Waring
53 Durnford Street
MIDDLETON
Manchester M24 3TZ.
*

Dr. Webb
213 Chestergate
STOCKPORT SK3 OAP.
* 1 case

Dr. R.J.A. Webb
53 Durnford Street
MIDDLETON
Manchester M24 3TZ.

Dr. R. Welton
The Clinic
UPPERMILL
Oldham
Lancs.
*

Dr. Weston
The Health Centre
LITTLEBOROUGH
Lancs.

Dr. E.E. Weston
279 Nuthurst Road
NEW MOSTON
Manchester.

Dr. T. Whitaker
Longsight Health Centre
526/528 Stockport Road
MANCHESTER M13 ORR.
*

Dr. C.R. Whitehouse
Rusholme Health Centre.

Dr. D. Wilde
Marjory Lees Health Centre
Egerton Street
OLDHAM
Lancs.
*

Dr. J. Wilkinson
Glodwick Health Centre
Glodwick Road
OLDHAM OL4 1YN.
* 1 case

Dr. R. Williamson
49 Fairfield Square
DROYLSDEN
Manchester.
*

Dr. F.O. Wilson
'Windward'
68 Worsley Road
WORSLEY
Manchester M28 4SN.

APPENDIX 3cIndividual List Sizes for G.P's Replying at 8 Months

Individual list sizes and shared list sizes for G.P's replying at 8 months

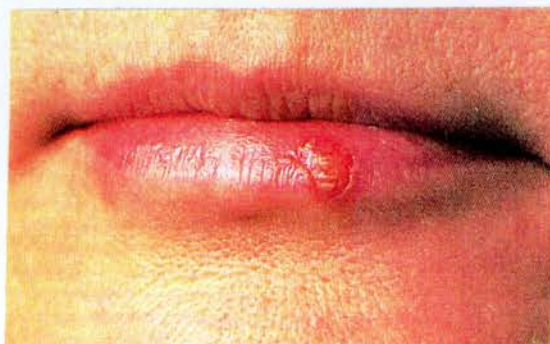
	<u>Bolton</u>	<u>Bury</u>	<u>Rochdale</u>	<u>Salford</u>	<u>Manchester</u>	<u>Oldham</u>	<u>Stockport</u>	<u>Tameside</u>
	1,700	2,459	2,470	400	?	?	2,100	?
	2,100	3,200	2,000	2,000	3,050	?	2,900	2,850
	2,000	2,700	2,500	2,600	1,822	1,500	2,600	2,950
	2,340	6,800	930	4,000	2,000	2,800	2,400	1,500
	6,000	2	2,500	2,000	2,175	3,400	3,160	2,500
	3,000	2,200	3,220	3,000	3,500	3,000	2,300	2,400
	3,900	5,100	1,440	1,200	2,400	1,000	1,060	1,900
	2,400	200	750	3,500	2,800	3,400	?	2,600
	13,000	1,000	600	1,400	2,300	1,126	500	2,800
	1,840	3,200	2,600	1,500	2,500	3,121	3,100	<u>2,500</u>
	2,900	4,200	2,802	3,800	780	2,936	2,800	
	2,200	2,500	4,550	1,600	?	2,700	2,800	
	?	2,200	3,500	?	900	2,100	2,792	
	2,500	4,000	2,200	7,900	635	2,100	1,800	
	2,600	1,086	3,000	<u>1,500</u>	1,300	2,800	3,490	
	2,500	3,800	1,375		7,500	3,500	2,300	
	7,000	<u>200</u>	1,200		2,500	1,700	2,800	
	1,600		800		5,000	<u>4,000</u>	<u>2,300</u>	
			2,700		3,100			
			2,300		1,800			
			2,000		3,000			
			3,000		1,750			
			<u>3,250</u>		7,500			
					2,100			
					<u>2,100</u>			
Total list size	<u>57,080</u>	<u>49,047</u>	<u>51,687</u>	<u>36,400</u>	<u>62,512</u>	<u>41,183</u>	<u>41,202</u>	<u>22,000</u>
Total G.P's	<u>18</u>	<u>17</u>	<u>23</u>	<u>15</u>	<u>25</u>	<u>18</u>	<u>18</u>	<u>10</u>

Total of list sizes = 361,111

77,850 total of shared list sizes given.

Appendix 4aPhotographs of Cold Sores

(shown to patients)



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Appendix 4b**MANCHESTER ROYAL INFIRMARY****POST MORTEM DECLARATION FORM**

Name of late patient Hosp. Record No.

Ward Consultant.

I do not object to a post mortem examination being carried out on the body of and I am not aware that he/she would have objected or that another surviving relative objects. I understand that this examination is carried out:—

(a) To verify the cause of death and to study the effects of treatment.

(b) To remove limited amounts of tissue for further study and for the treatment of other patients.

Signed

Relationship to Deceased

Witnessed by

Date

I agree to the removal of the eyes from the said body for the purpose of corneal grafts.

Signed

Date

APPENDIX 4c

THE EFFECT OF NALOXONE ON SKIN REACTIONS TO INTRADERMAL INJECTIONS OF HUMAN RECOMBINANT INTERFERON $\alpha 2$

Table: Mean Area of Erythema and Mean Flare Intensity Score n = 5

time	5.10 ⁵ U (0.1 ml) of IFN intradermally				the same after pretreatment with 1 ml (0.4 mg) of naloxone subcutaneously			
	mean area (mm ²)	min area (mm ²)	max area (mm ²)	mean flare intensity (0-3)	mean area (mm ²)	min area (mm ²)	max area (mm ²)	mean flare intensity (0-3)
5min	385	283	491	2.6	371	165	668	2.8
10	265	130	449	2.6	267	79	566	2.2
15	180	118	265	2.0	179	71	393	2.0
20	124	97	236	1.6	156	71	393	1.8
25	105	63	181	1.2	132	64	361	1.2
30	75	38	126	1.2	86	47	163	1.2
35	46	0	82	0.8	45	0	132	0.8
40	27	0	63	0.6	34	0	123	0.4
45	0	0	0	0.0	19	0	95	0.2
50	0	0	0	0.0	17	0	86	0.2
55	0	0	0	0.0	0	0	0	0.0
60	0	0	0	0.0	0	0	0	0.0
2h	0	0	0	0.0	0	0	0	0.0
4h	0	0	0	0.0	0	0	0	0.0
8h	181	0	471	1.0	75	0	198	0.4

SUMMARY

There is a certain homology between interferon and opioids. Both are known to cause skin reactions. We measured the flare reactions to an intradermal injection of a pure recombinant interferon α in 5 patients with laryngeal papilloma and repeated this three days later after pretreatment with naloxone a specific opioid antagonist. Naloxone did not reduce the immediate reactions, but appeared to reduce the faint late reactions 8 hours after injection in 3 of the 5 patients.

Method derived from Scott et al. 1980.

Appendix 4d - Cocultivation Study - Data Sheet

NAME DATE CODE

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CAUSE OF DEATH

AGE HOURS AFTER DEATH

GANGLION SIDE

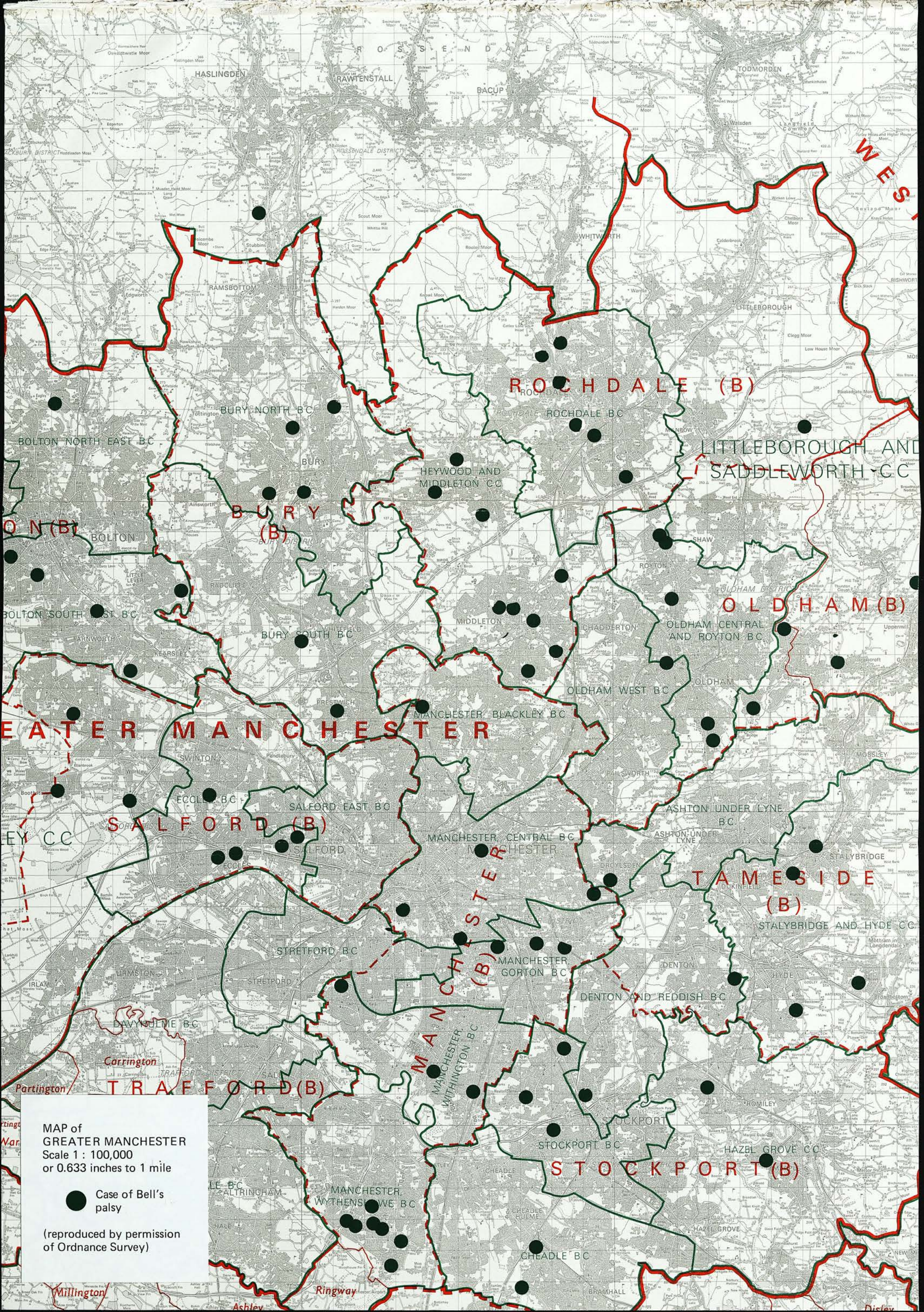
		<u>OBSERVED</u>	<u>M/C</u>	<u>COMMENTS</u>
WEEK 1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
V1				
V2				
V3				
V4				

TRANSFER DATES ISOLATE POSITIVE/NEGATIVE

GANGLION SIDE

		<u>OBSERVED</u>	<u>M/C</u>	<u>COMMENTS</u>
WEEK 1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
V1				
V2				
V3				
V4				

TRANSFER DATES ISOLATE POSITIVE/NEGATIVE



MAP of
GREATER MANCHESTER
Scale 1 : 100,000
or 0.633 inches to 1 mile

● Case of Bell's
palsy

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of Ordnance Survey)